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JC682 U.S. PRO
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Sir:

Transmitted herewith for filing is the continuation-in-part patent application of

Inventor(s): Kenneth Rhodes, Maria Betty, Huai-Ping Ling, and Wenqian An

For: POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR

Enclosed are:

This is a request for filing a continuation-in-part divisional application under 37 CFR 1.53(b), of pending prior application serial no. 09/399,913, filed on September 21, 1999 entitled POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR.

- 148 pages of specification, 14 pages of claims, 1 page of abstract.
- 48 sheets of formal drawings (Figures 1-43).
- An unexecuted Declaration, Petition and Power of Attorney.
- 92 pages of sequence listing (numbered 1-92).
- Transmittal Letter for Diskette of Sequence Listing.
- Diskette Containing Sequence Listing.
- Statement of Limited Recognition Under 37 C.F.R. §10.9(b)

The filing fee has been calculated as shown below:

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INDEP. CLAIMS	2 - 3	=0
<input checked="" type="checkbox"/> MULTIPLE DEPENDENT CLAIMS PRESENTED		

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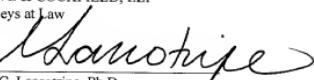
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- Address all future communications (May only be completed by applicant, or attorney or agent of record) to Amy E. Mandragouras at Customer Number: 000959 whose address is:

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POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR**Related Applications**

- This application claims priority to U.S. provisional Application No. 60/110,033, filed on November 25, 1998, U.S. provisional Application No. 60/109,333, filed on November 20, 1998, U.S. provisional Application No. 60/110,277, filed on November 30, 1998, U.S. Patent Application No.: 09/298,731, filed on April 23, 1999, U.S. Patent Application No.: 09/350,614, filed on July 9, 1999, U.S. Patent Application No.: 09/350,874, filed on July 9, 1999, U.S. Patent Application No.: 09/399,913, filed on September 21, 1999, U.S. Patent Application No.: 09/400,492, filed on September 21, 1999, and PCT Application No. PCT/US99/27428, filed on November 19, 1999, incorporated herein in their entirety by this reference.

Background of the Invention

- Mammalian cell membranes are important to the structural integrity and activity of many cells and tissues. Of particular interest in membrane physiology is the study of trans-membrane ion channels which act to directly control a variety of pharmacological, physiological, and cellular processes. Numerous ion channels have been identified including calcium, sodium, and potassium channels, each of which have been investigated to determine their roles in vertebrate and insect cells.

Because of their involvement in maintaining normal cellular homeostasis, much attention has been given to potassium channels. A number of these potassium channels open in response to changes in the cell membrane potential. Many voltage-gated potassium channels have been identified and characterized by their electrophysiological and pharmacological properties. Potassium currents are more diverse than sodium or calcium currents and are further involved in determining the response of a cell to external stimuli. The diversity of potassium channels and their important physiological role highlights their potential as targets for developing therapeutic agents for various diseases.

One of the best characterized classes of potassium channels are the voltage-gated potassium channels. The prototypical member of this class is the protein encoded by the Shaker gene in *Drosophila melanogaster*. Proteins of the Shal or Kv4 family are a type of voltage-gated potassium channels that underlies many of the native A type currents that have been recorded from different primary cells. Kv4 channels have a major role in

the repolarization of cardiac action potentials. In neurons, Kv4 channels and the A currents they may comprise play an important role in modulation of firing rate, action potential initiation and in controlling dendritic responses to synaptic inputs.

- The fundamental function of a neuron is to receive, conduct, and transmit
- 5 signals. Despite the varied purpose of the signals carried by different classes of neurons, the form of the signal is always the same and consists of changes in the electrical potential across the plasma membrane of the neuron. The plasma membrane of a neuron contains voltage-gated cation channels, which are responsible for propagating this electrical potential (also referred to as an action potential or nerve impulse) across and
- 10 along the plasma membrane.

The Kv family of channels includes, among others: (1) the delayed-rectifier potassium channels, which repolarize the membrane after each action potential to prepare the cell to fire again; and (2) the rapidly inactivating (A-type) potassium channels, which are active predominantly at subthreshold voltages and act to reduce

15 the rate at which excitable cells reach firing threshold. In addition to being critical for action potential conduction, Kv channels also control the response to depolarizing, e.g., synaptic, inputs and play a role in neurotransmitter release. As a result of these activities, voltage-gated potassium channels are key regulators of neuronal excitability (Hille B., Ionic Channels of Excitable Membranes, Second Edition, Sunderland, MA:

20 Sinauer, (1992)).

There is tremendous structural and functional diversity within the Kv potassium channel superfamily. This diversity is generated both by the existence of multiple genes and by alternative splicing of RNA transcripts produced from the same gene. Nonetheless, the amino acid sequences of the known Kv potassium channels show high

25 similarity. All appear to be comprised of four, pore forming α -subunits and some are known to have four cytoplasmic (β -subunit) polypeptides (Jan L.Y. et al. (1990) *Trends Neurosci* 13:415-419, and Pongs, O. et al. (1995) *Sem Neurosci*. 7:137-146). The known Kv channel (α -subunits fall into four sub-families named for their homology to channels first isolated from *Drosophila*: the Kv1, or *Shaker*-related subfamily; the Kv2,

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or *Shab*-related subfamily; the Kv3, or *Shaw*-related subfamily; and the Kv4, or *Shal*-related subfamily.

Kv4.2 and Kv4.3 are examples of Kv channel (α -subunits of the *Shal*-related subfamily. Kv4.3 has a unique neuroanatomical distribution in that its mRNA is highly expressed in brainstem monoaminergic and forebrain cholinergic neurons, where it is involved in the release of the neurotransmitters dopamine, norepinephrine, serotonin, and acetylcholine.

This channel is also highly expressed in cortical pyramidal cells and in interneurons. (Serdio P. et al. (1996) *J. Neurophys* 75:2174-2179). Interestingly, the Kv4.3 polypeptide is highly expressed in neurons which express the corresponding mRNA. The Kv4.3 polypeptide is expressed in the somatodendritic membranes of these cells, where it is thought to contribute to the rapidly inactivating K⁺ conductance. Kv4.2 mRNA is widely expressed in brain, and the corresponding polypeptide also appears to be concentrated in somatodendritic membranes where it also contributes to the rapidly inactivating K⁺ conductance (Sheng et al. (1992) *Neuron* 9:271-84). These somatodendritic A-type Kv channels, like Kv4.2 and Kv4.3, are likely involved in processes which underlie learning and memory, such as integration of sub-threshold synaptic responses and the conductance of back-propagating action potentials (Hoffman D.A. et al. (1997) *Nature* 387:869-875).

Thus, proteins which interact with and modulate the activity of potassium channel proteins e.g., potassium channels having a Kv4.2 or Kv4.3 subunit, provide novel molecular targets to modulate neuronal or cardiac excitability, e.g., action potential conduction, somatodendritic excitability and neurotransmitter release, in cells expressing these channels. In addition, detection of genetic lesions in the gene encoding these proteins could be used to diagnose and treat central nervous system disorders such as epilepsy, spinocerebellar ataxia, anxiety, depression, age-related memory loss, migraine, obesity, Parkinsons disease or Alzheimer's disease; or cardiovascular disorders such as heart failure, hypertension, atrial fibrillation, dilated cardiomyopathy, idiopathic cardiomyopathy, or angina.

Summary of the Invention

The present invention is based, at least in part, on the discovery of novel nucleic acid molecules which encode gene products that interact with potassium channel proteins or possess substantial homology to the gene products of the invention that

- 5 interact with potassium channel proteins (paralogs). Potassium channel proteins are, for example, potassium channels having a Kv4.2 or Kv4.3 subunit. The nucleic acid molecules of the invention and their gene products are referred to herein as "Potassium Channel Interacting Proteins", "PCIP", or "KChIP" nucleic acid and protein molecules. The PCIP proteins of the present invention interact with, *e.g.*, bind to a potassium
- 10 channel protein, modulate the activity of a potassium channel protein, and/or modulate a potassium channel mediated activity in a cell, *e.g.*, a neuronal or cardiac cell. The PCIP molecules of the present invention are useful as modulating agents to regulate a variety of cellular processes, *e.g.*, neuronal or cardiac cell processes. Accordingly, in one aspect, this invention provides isolated nucleic acid molecules encoding PCIP proteins
- 15 or biologically active portions thereof, as well as nucleic acid fragments suitable as primers or hybridization probes for the detection of PCIP-encoding nucleic acids.

- In one embodiment, a PCIP nucleic acid molecule of the invention is at least 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more identical to the nucleotide sequence (*e.g.*, to the entire length of the nucleotide sequence) shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a complement thereof.

- In another preferred embodiment, the isolated nucleic acid molecule includes the nucleotide sequence shown SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ

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ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID

- 5 NO:71, or a complement thereof. In another preferred embodiment, the nucleic acid molecule includes a fragment of at least 300, 350, 400, 426, 471, or 583 nucleotides of the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID
10 NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or a complement thereof.

In another embodiment, a PCIP nucleic acid molecule includes a nucleotide

- 15 sequence encoding a protein having an amino acid sequence sufficiently identical to the
amino acid sequence of SEQ ID NO: 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8,
SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ
ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID
NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID
20 NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID
NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or an amino acid sequence
encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number
98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946,
98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In a preferred
25 embodiment, a PCIP nucleic acid molecule includes a nucleotide sequence encoding a
protein having an amino acid sequence at least 50%, 55%, 60%, 65%, 70%, 75%, 80%,
85%, 90%, 95% or more identical to the amino acid sequence of SEQ ID NO: 2, SEQ ID
NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14,
SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ
30 ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID
NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID

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NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or

5 98994.

In another preferred embodiment, an isolated nucleic acid molecule encodes the amino acid sequence of 1v, 9q, p19, W28559, KChIP4a, KChIP4b, 33b07, 1p, and rat 7s protein. In yet another preferred embodiment, the nucleic acid molecule includes a nucleotide sequence encoding a protein having the amino acid sequence of SEQ ID NO: 10 2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 15 98994. In yet another preferred embodiment, the nucleic acid molecule is at least 426, 471, or 583 nucleotides in length and encodes a protein having 20 a PCIP activity (as described herein).

Another embodiment of the invention features nucleic acid molecules, preferably PCIP nucleic acid molecules, which specifically detect PCIP nucleic acid molecules relative to nucleic acid molecules encoding non-PCIP proteins. For example, in one embodiment, such a nucleic acid molecule is at least 426, 400-450, 471, 450-500, 500-25 550, 583, 550-600, 600-650, 650-700, 700-750, 750-800 or more nucleotides in length and hybridizes under stringent conditions to a nucleic acid molecule comprising the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ 30 ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID

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- NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or 5 a complement thereof. In preferred embodiments, the nucleic acid molecules are at least 15 (e.g., contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 93-126, 360-462, 732-825, 1028-1054, or 1517-1534 of SEQ ID NO:7. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 93-126, 360-462, 732-825, 1028-1054, or 1517-1534 of SEQ ID NO:7.
- 10 In other preferred embodiments, the nucleic acid molecules are at least 15 (e.g., contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 1-14, 49-116, 137-311, 345-410, 430-482, 503-518, 662-693, 1406-1421, 1441-1457, 1478-1494, or 1882-1959 of SEQ ID NO:13. In other preferred embodiments, the 15 nucleic acid molecules comprise nucleotides 1-14, 49-116, 137-311, 345-410, 430-482, 503-518, 662-693, 1406-1421, 1441-1457, 1478-1494, or 1882-1959 of SEQ ID NO:13. In preferred embodiments, the nucleic acid molecules are at least 15 (e.g., contiguous) nucleotides in length and hybridize under stringent conditions to nucleotides 932-1527, 1548-1765, 1786-1871, 1908-2091, 2259-2265, or 2630-2654 of SEQ ID 20 NO:35. In other preferred embodiments, the nucleic acid molecules comprise nucleotides 932-1527, 1548-1765, 1786-1871, 1908-2091, 2259-2265, or 2630-2654 of SEQ ID NO:35.
- In other preferred embodiments, the nucleic acid molecule encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, 25 SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the 30 plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950,

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98951, 98991, 98993, or 98994, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ
5 ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 under stringent conditions.

Another embodiment of the invention provides an isolated nucleic acid molecule
10 which is antisense to a PCIP nucleic acid molecule, *e.g.*, the coding strand of a PCIP nucleic acid molecule.

Another aspect of the invention provides a vector comprising a PCIP nucleic acid molecule. In certain embodiments, the vector is a recombinant expression vector. In another embodiment, the invention provides a host cell containing a vector of the
15 invention. The invention also provides a method for producing a protein, preferably a PCIP protein, by culturing in a suitable medium, a host cell, *e.g.*, a mammalian host cell such as a non-human mammalian cell, of the invention containing a recombinant expression vector, such that the protein is produced.

Another aspect of this invention features isolated or recombinant PCIP proteins
20 and polypeptides. In one embodiment, the isolated protein, preferably a PCIP protein, includes at least one calcium binding domain. In a preferred embodiment, the protein, preferably a PCIP protein, includes at least one calcium binding domain and has an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ
25 ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or the amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942,

98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another preferred embodiment, the protein, preferably a PCIP protein, includes at least one calcium binding domain and modulates a potassium channel mediated activity. In yet another preferred embodiment, the protein, preferably a PCIP 5 protein, includes at least one calcium binding domain and is encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ 10 ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71.

In another embodiment, the invention features fragments of the proteins having 15 the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID 20 NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, wherein the fragment comprises at least 15 amino acids (*e.g.*, contiguous amino acids) of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID 25 NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, or an amino acid sequence encoded by the DNA insert of the plasmid deposited with the ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another 30 embodiment, the protein, preferably a PCIP protein, has the amino acid sequence of

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- SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID 5 NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

In another embodiment, the invention features an isolated protein, preferably a PCIP protein, which is encoded by a nucleic acid molecule having a nucleotide sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more 10 identical to a nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID 15 NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or a complement thereof.

The proteins of the present invention or biologically active portions thereof, can be operatively linked to a non-PCIP polypeptide (e.g., heterologous amino acid sequences) to form fusion proteins. The invention further features antibodies, such as 20 monoclonal or polyclonal antibodies, that specifically bind proteins of the invention, preferably PCIP proteins. In addition, the PCIP proteins or biologically active portions thereof can be incorporated into pharmaceutical compositions, which optionally include pharmaceutically acceptable carriers.

In another aspect, the present invention provides a method for detecting the 25 presence of a PCIP nucleic acid molecule, protein or polypeptide in a biological sample by contacting the biological sample with an agent capable of detecting a PCIP nucleic acid molecule, protein or polypeptide such that the presence of a PCIP nucleic acid molecule, protein or polypeptide is detected in the biological sample.

In another aspect, the present invention provides a method for detecting the 30 presence of PCIP activity in a biological sample by contacting the biological sample

with an agent capable of detecting an indicator of PCIP activity such that the presence of PCIP activity is detected in the biological sample.

In another aspect, the invention provides a method for modulating PCIP activity comprising contacting a cell capable of expressing PCIP with an agent that modulates 5 PCIP activity such that PCIP activity in the cell is modulated. In one embodiment, the agent inhibits PCIP activity. In another embodiment, the agent stimulates PCIP activity. In one embodiment, the agent is an antibody that specifically binds to a PCIP protein. In another embodiment, the agent modulates expression of PCIP by modulating transcription of a PCIP gene or translation of a PCIP mRNA. In yet another 10 embodiment, the agent is a nucleic acid molecule having a nucleotide sequence that is antisense to the coding strand of a PCIP mRNA or a PCIP gene.

In one embodiment, the methods of the present invention are used to treat a subject having a disorder characterized by aberrant PCIP protein or nucleic acid expression or activity by administering an agent which is a PCIP modulator to the 15 subject. In one embodiment, the PCIP modulator is a PCIP protein. In another embodiment the PCIP modulator is a PCIP nucleic acid molecule. In yet another embodiment, the PCIP modulator is a peptide, peptidomimetic, or other small molecule. In a preferred embodiment, the disorder characterized by aberrant PCIP protein or nucleic acid expression is a CNS disorder or a cardiovascular disorder.

20 The present invention also provides a diagnostic assay for identifying the presence or absence of a genetic alteration characterized by at least one of (i) aberrant modification or mutation of a gene encoding a PCIP protein; (ii) mis-regulation of the gene; and (iii) aberrant post-translational modification of a PCIP protein, wherein a wild-type form of the gene encodes a protein with a PCIP activity.

25 In another aspect the invention provides a method for identifying a compound that binds to or modulates the activity of a PCIP protein, by providing an indicator composition comprising a PCIP protein having PCIP activity, contacting the indicator composition with a test compound, and determining the effect of the test compound on PCIP activity in the indicator composition to identify a compound that modulates the 30 activity of a PCIP protein.

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Other features and advantages of the invention will be apparent from the following detailed description and claims.

Brief Description of the Drawings

5 *Figure 1* depicts the cDNA sequence and predicted amino acid sequence of human 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1463 of SEQ ID NO:1. The amino acid sequence corresponds to amino acids 1 to 216 of SEQ ID NO:2.

Figure 2 depicts the cDNA sequence and predicted amino acid sequence of rat 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1856 of SEQ ID NO:3.

10 The amino acid sequence corresponds to amino acids 1 to 245 of SEQ ID NO:4.

Figure 3 depicts the cDNA sequence and predicted amino acid sequence of mouse 1v. The nucleotide sequence corresponds to nucleic acids 1 to 1907 of SEQ ID NO:5. The amino acid sequence corresponds to amino acids 1 to 216 of SEQ ID NO:6.

15 *Figure 4* depicts the cDNA sequence and predicted amino acid sequence of rat 1vl. The nucleotide sequence corresponds to nucleic acids 1 to 1534 of SEQ ID NO:7. The amino acid sequence corresponds to amino acids 1 to 227 of SEQ ID NO:8.

Figure 5 depicts the cDNA sequence and predicted amino acid sequence of mouse 1vl. The nucleotide sequence corresponds to nucleic acids 1 to 1540 of SEQ ID NO:9. The amino acid sequence corresponds to amino acids 1 to 227 of SEQ ID NO:10.

20 *Figure 6* depicts the cDNA sequence and predicted amino acid sequence of rat 1vn. The nucleotide sequence corresponds to nucleic acids 1 to 955 of SEQ ID NO:11. The amino acid sequence corresponds to amino acids 1 to 203 of SEQ ID NO:12.

25 *Figure 7* depicts the cDNA sequence and predicted amino acid sequence of human 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 2009 of SEQ ID NO:13. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:14.

Figure 8 depicts the cDNA sequence and predicted amino acid sequence of rat 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 1247 of SEQ ID NO:15. The amino acid sequence corresponds to amino acids 1 to 257 of SEQ ID NO:16.

30 *Figure 9* depicts the cDNA sequence and predicted amino acid sequence of mouse 9ql. The nucleotide sequence corresponds to nucleic acids 1 to 2343 of SEQ ID

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NO:17. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:18.

- Figure 10* depicts the cDNA sequence and predicted amino acid sequence of human 9qm. The nucleotide sequence corresponds to nucleic acids 1 to 1955 of SEQ ID NO:19. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:20.

- Figure 11* depicts the cDNA sequence and predicted amino acid sequence of rat 9qm. The nucleotide sequence corresponds to nucleic acids 1 to 2300 of SEQ ID NO:21. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:22.

- Figure 12* depicts the cDNA sequence and predicted amino acid sequence of human 9qs. The nucleotide sequence corresponds to nucleic acids 1 to 1859 of SEQ ID NO:23. The amino acid sequence corresponds to amino acids 1 to 220 of SEQ ID NO:24.

- 15 *Figure 13* depicts the cDNA sequence and predicted amino acid sequence of monkey 9qs. The nucleotide sequence corresponds to nucleic acids 1 to 2191 of SEQ ID NO:25. The amino acid sequence corresponds to amino acids 1 to 220 of SEQ ID NO:26.

- 20 *Figure 14* depicts the cDNA sequence and predicted amino acid sequence of rat 9qc. The nucleotide sequence corresponds to nucleic acids 1 to 2057 of SEQ ID NO:27. The amino acid sequence corresponds to amino acids 1 to 252 of SEQ ID NO:28.

- 25 *Figure 15* depicts the cDNA sequence and predicted amino acid sequence of rat 8t. The nucleotide sequence corresponds to nucleic acids 1 to 1904 of SEQ ID NO:29. The amino acid sequence corresponds to amino acids 1 to 225 of SEQ ID NO:30.

- 25 *Figure 16* depicts the cDNA sequence and predicted amino acid sequence of human p19. The nucleotide sequence corresponds to nucleic acids 1 to 619 of SEQ ID NO:31. The amino acid sequence corresponds to amino acids 1 to 200 of SEQ ID NO:32.

- 30 *Figure 17* depicts the cDNA sequence and predicted amino acid sequence of rat p19. The nucleotide sequence corresponds to nucleic acids 1 to 442 of SEQ ID NO:33. The amino acid sequence corresponds to amino acids 1 to 109 of SEQ ID NO:34.

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Figure 18 depicts the cDNA sequence and predicted amino acid sequence of mouse p19. The nucleotide sequence corresponds to nucleic acids 1 to 2644 of SEQ ID NO:35. The amino acid sequence corresponds to amino acids 1 to 256 of SEQ ID NO:36.

5 Figure 19 depicts the cDNA sequence and predicted amino acid sequence of human W28559. The nucleotide sequence corresponds to nucleic acids 1 to 380 of SEQ ID NO:37. The amino acid sequence corresponds to amino acids 1 to 126 of SEQ ID NO:38.

10 Figure 20 depicts the cDNA sequence and predicted amino acid sequence of human P193. The nucleotide sequence corresponds to nucleic acids 1 to 2176 of SEQ ID NO:39. The amino acid sequence corresponds to amino acids 1 to 41 of SEQ ID NO:40.

15 Figure 21 depicts a schematic representation of the rat 1v, the rat 9qm, and the mouse P19 proteins, aligned to indicate the conserved domains among these proteins.
15 Figure 22 depicts the genomic DNA sequence of human 9q. Figure 22A depicts exon 1 and its flanking intron sequences (SEQ ID NO:46). Figure 22B depicts exons 2-11 and the flanking intron sequences (SEQ ID NO:47).

20 Figure 23 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4a. The nucleotide sequence corresponds to nucleic acids 1 to 2413 of SEQ ID NO:48. The amino acid sequence corresponds to amino acids 1 to 233 of SEQ ID NO:49.

25 Figure 24 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4b. The nucleotide sequence corresponds to nucleic acids 1 to 1591 of SEQ ID NO:50. The amino acid sequence corresponds to amino acids 1 to 233 of SEQ ID NO:51.

Figure 25 depicts an alignment of KChIP4a, KChIP4b, 9ql, 1v, p19, and related human paralog (hsncspara) W28559. Amino acids identical to the consensus are shaded in black, conserved amino acids are shaded in gray.

30 Figure 26 depicts the cDNA sequence and predicted amino acid sequence of rat 33b07. The nucleotide sequence corresponds to nucleic acids 1 to 2051 of SEQ ID

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NO:52. The amino acid sequence corresponds to amino acids 1 to 407 of SEQ ID NO:53.

- Figure 27 depicts the cDNA sequence and predicted amino acid sequence of human 33b07. The nucleotide sequence corresponds to nucleic acids 1 to 4148 of SEQ ID NO:54. The amino acid sequence corresponds to amino acids 1 to 414 of SEQ ID NO:55.

Figure 28 depicts the cDNA sequence and predicted amino acid sequence of rat 1p. The nucleotide sequence corresponds to nucleic acids 1 to 2643 of SEQ ID NO:56. The amino acid sequence corresponds to amino acids 1 to 267 of SEQ ID NO:57.

- Figure 29 depicts the cDNA sequence and predicted amino acid sequence of rat 7s. The nucleotide sequence corresponds to nucleic acids 1 to 2929 of SEQ ID NO:58. The amino acid sequence corresponds to amino acids 1 to 270 of SEQ ID NO:59.

- Figure 30 depicts the cDNA sequence and predicted amino acid sequence of rat 29x. The nucleotide sequence corresponds to nucleic acids 1 to 1489 of SEQ ID NO:60. The amino acid sequence corresponds to amino acids 1 to 351 of SEQ ID NO:61.

Figure 31 depicts the cDNA sequence of rat 25r. The nucleotide sequence corresponds to nucleic acids 1 to 1194 of SEQ ID NO:62.

- Figure 32 depicts the cDNA sequence and predicted amino acid sequence of rat 5p. The nucleotide sequence corresponds to nucleic acids 1 to 600 of SEQ ID NO:63. The amino acid sequence corresponds to amino acids 1 to 95 of SEQ ID NO:64.

Figure 33 depicts the cDNA sequence and predicted amino acid sequence of rat 7q. The nucleotide sequence corresponds to nucleic acids 1 to 639 of SEQ ID NO:65. The amino acid sequence corresponds to amino acids 1 to 212 of SEQ ID NO:66.

- Figure 34 depicts the cDNA sequence and predicted amino acid sequence of rat 19r. The nucleotide sequence corresponds to nucleic acids 1 to 816 of SEQ ID NO:67. The amino acid sequence corresponds to amino acids 1 to 271 of SEQ ID NO:68.

- Figure 35 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4c. The nucleotide sequence corresponds to nucleic acids 1 to 2263 of SEQ ID NO:69. The amino acid sequence corresponds to amino acids 1 to 229 of SEQ ID NO:70.

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Figure 36 depicts the cDNA sequence and predicted amino acid sequence of monkey KChIP4d. The nucleotide sequence corresponds to nucleic acids 1 to 2259 of SEQ ID NO:71. The amino acid sequence corresponds to amino acids 1 to 250 of SEQ ID NO:72.

5 *Figure 37* depicts an alignment of KChIP4a, KChIP4b, KChIP4c, and KChIP4d.

Figure 38 depicts a graph showing the current traces from CHO cells which express Kv4.2 with or without KChIP2 (9ql). Cells are voltage clamped at -80 mV and stepped from -60 mV to +50 mV for 200ms. Peak current amplitudes at the various test voltages are shown in the right panel. *Figure 38* further depicts a table showing the 10 amplitude and kinetic effects of KChIP2 (9ql) on Kv4.2. KChIP2 expression alters the peak current amplitude, inactivation and recovery from inactivation time constants, and activation $V_{1/2}$.

15 *Figure 39* depicts a graph showing the current traces from CHO cells which express Kv4.2 with or without KChIP3 (p19). Cells are voltage clamped at -80 mV and stepped from -60 mV to +50 mV for 200ms. Peak current amplitudes at the various test voltages are shown in the right panel. *Figure 39* further depicts a table showing the amplitude and kinetic effects of KChIP3 (p19) on Kv4.2. KChIP3 causes alterations in peak current and inactivation and recovery from inactivation time constants.

20 *Figure 40* depicts results from electrophysiological experiments demonstrating that coexpression of KChIP1 dramatically alters the current density and kinetics of Kv4.2 channels expressed in CHO cells.

25 *Figure 40A* depicts current traces from a Kv4.2 transfected CHO cell. Current was evoked by depolarizing the cell sequentially from a holding potential of -80 mV to test potentials from -60 to 50 mV. Current traces are leak subtracted using a p/5 protocol. The current axis is shown at the same magnification as in (b) to emphasize the change in current amplitudes. Inset- Single current trace at 50mV at an expanded current axis to show the kinetics of current activation and inactivation.

Figure 40B depicts current traces as in (a), but from a cell transfected with equal amounts of DNA for Kv4.2 and KChIP1.

30 *Figure 40C* depicts peak current amplitude at all voltages from cells transfected with Kv4.2 alone (n=11) or cotransfected with KChIP1 (n=9).

Figures 40D and 40E depict recovery from inactivation using a two pulse protocol. Kv4.2 alone (D) or coexpressed with KChIP1 (E) is driven into the inactivated state using a first pulse to 50 mV, then a second pulse to 50 mV is applied at varying times after the first pulse. Holding potential is -80 mV before and after all pulses.

- 5 *Figure 40F* depicts a summary of the percentage the peak current recovers between pulses for Kv4.2 (n=8) and Kv4.2 plus KChIP1 (n=5) transfected cells. The time constant of recovery from inactivation is fit to a single exponential.

10 *Figure 41* depicts an alignment of human KChIP family members with closely related members of the recoverin family of Ca 2+ sensing proteins. (HIP:human hippocalcin; NCS1:rat neuronal calcium sensor 1). The alignment was performed using the MegAlign program for Macintosh (version 4.00 from DNASTAR) using the Clustal method with the PAM250 residue weight table and default parameters, and shaded using BOXSHADES. Residues identical to the consensus are shaded black, conservative substitutions are shaded grey. X, Y, Z and -X, -Y, -Z denote the positions of residues 15 which are responsible for binding to the calcium ion in the EF hand.

Figure 42 depicts a physical map of the IOSCA region.

Figure 43 depicts a linkage map showing the location of h9q and known markers associating with IOSCA and epilepsy.

20 **Detailed Description of the Invention**

The present invention is based, at least in part, on the discovery of novel nucleic acid molecules which encode gene products that interact with potassium channel proteins or possess substantial homology to the gene products of the invention that interact with potassium channel proteins (paralogs). Potassium channel proteins are, for 25 example, potassium channels having a Kv4.2 or Kv4.3 subunit. The nucleic acid molecules of the invention and their gene products are referred to herein as "Potassium Channel Interacting Proteins", "PCIP", or "KChIP" nucleic acid and protein molecules. Preferably, the PCIP proteins of the present invention interact with, e.g., bind to a potassium channel protein, modulate the activity of a potassium channel protein, and/or 30 modulate a potassium channel mediated activity in a cell, e.g., a neuronal or cardiac cell.

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As used herein, the term "PCIP family" when referring to the protein and nucleic acid molecules of the invention is intended to mean two or more proteins or nucleic acid molecules having a PCIP activity as defined herein. Such PCIP family members can be naturally or non-naturally occurring and can be from either the same or different species.

- 5 For example, a PCIP family can contain a first protein of human origin, as well as other, distinct proteins of human origin or alternatively, can contain homologues of non-human origin.

As used interchangeably herein, a "PCIP activity", "biological activity of PCIP" or "functional activity of PCIP", refers to an activity exerted by a PCIP protein,

- 10 polypeptide or nucleic acid molecule on a PCIP responsive cell or on a PCIP protein substrate, as determined *in vivo*, or *in vitro*, according to standard techniques. In one embodiment, a PCIP activity is a direct activity, such as an association with a PCIP-target molecule. As used herein, a "target molecule" or "binding partner" is a molecule with which a PCIP protein binds or interacts in nature, such that PCIP-mediated function
15 is achieved. A PCIP target molecule can be a non-PCIP molecule or a PCIP protein or polypeptide of the present invention. In an exemplary embodiment, a PCIP target molecule is a PCIP ligand. Alternatively, a PCIP activity is an indirect activity, such as a cellular signaling activity mediated by interaction of the PCIP protein with a PCIP ligand. The biological activities of PCIP are described herein.

- 20 For example, the PCIP proteins of the present invention can have one or more of the following activities: (1) they can interact with (*e.g.*, bind to) a potassium channel protein or portion thereof; (2) they can regulate the phosphorylation state of a potassium channel protein or portion thereof; (3) they can associate with (*e.g.*, bind) calcium and can, for example, act as calcium dependent kinases, *e.g.*, phosphorylate a potassium
25 channel or a G-protein coupled receptor in a calcium-dependent manner; (4) they can associate with (*e.g.*, bind) calcium and can, for example, act in a calcium-dependent manner in cellular processes, *e.g.*, act as calcium dependent transcription factors; (5) they can modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal cell such as a sensory neuron cell or a motor neuron cell, or a cardiac cell) to, for example,
30 beneficially affect the cell; (6) they can modulate chromatin formation in a cell, *e.g.*, a neuronal or cardiac cell; (7) they can modulate vesicular traffic and protein transport in a

cell, e.g., a neuronal or cardiac cell; (8) they can modulate cytokine signaling in a cell, e.g., a neuronal or cardiac cell; (9) they can regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (10) they can modulate cellular proliferation; (11) they can modulate the release of neurotransmitters; (12) they can modulate membrane excitability; (13) they can influence the resting potential of membranes; (14) they can modulate wave forms and frequencies of action potentials; and (15) they can modulate thresholds of excitation.

As used herein, a "potassium channel" includes a protein or polypeptide that is involved in receiving, conducting, and transmitting signals in an excitable cell.

10 Potassium channels are typically expressed in electrically excitable cells, e.g., neurons, cardiac, skeletal and smooth muscle, renal, endocrine, and egg cells, and can form heteromultimeric structures, e.g., composed of pore-forming and cytoplasmic subunits. Examples of potassium channels include: (1) the voltage-gated potassium channels, (2) the ligand-gated potassium channels, and (3) the mechanically-gated potassium channels. For a detailed description of potassium channels, see Kandel E.R. et al., Principles of Neural Science, second edition, (Elsevier Science Publishing Co., Inc., N.Y. (1985)), the contents of which are incorporated herein by reference. The PCIP proteins of the present invention have been shown to interact with, for example, potassium channels having a Kv4.3 subunit or a Kv4.2 subunit.

20 As used herein, a "potassium channel mediated activity" includes an activity which involves a potassium channel, e.g., a potassium channel in a neuronal cell or a cardiac cell, associated with receiving, conducting, and transmitting signals in, for example, the nervous system or in the heart. Potassium channel mediated activities include release of neurotransmitters, e.g., dopamine or norepinephrine, from cells, e.g., 25 neuronal or cardiac cells; modulation of resting potential of membranes, wave forms and frequencies of action potentials, and thresholds of excitation; and modulation of processes such as integration of sub-threshold synaptic responses and the conductance of back-propagating action potentials in, for example, neuronal cells or cardiac cells.

As the PCIP proteins of the present invention modulate potassium channel mediated activities, they may be useful as novel diagnostic and therapeutic agents for potassium channel associated disorders and/or nervous system related disorders.

Moreover, the PCIP proteins of the present invention modulate Kv4 potassium channels, e.g., potassium channels having a Kv4.2 or Kv4.3 subunit, which underlie the voltage-gated K⁺ current known as I_{to} (transient outward current) in the mammalian heart (Kaab S. et al. (1998) *Circulation* 98(14):1383-93; Dixon J.E. et al. (1996) *Circulation Research* 79(4):659-68; Nerbonne JM (1998) *Journal of Neurobiology* 37(1):37-59; Barry D.M. et al. (1998) *Circulation Research* 83(5):560-7; Barry D.M. et al. (1996) *Annual Review of Physiology* 58:363-94. This current underlies the rapid repolarization of cardiac myocytes during an action potential. It also participates in the inter-beat interval by controlling the rate at which cardiac myocytes reach the threshold for firing a subsequent action potential.

This current is also known to be down regulated in patients with cardiac hypertrophy, resulting in prolongation of the cardiac action potential. In these patients, action potential prolongation is thought to produce changes in calcium load and calcium handling within the myocardium, which contributes to the progression of cardiac disease from hypertrophy to heart failure (Wickenden et al. (1998) *Cardiovascular Research* 37:312). Interestingly, several PCIPs of the present invention (e.g., 9ql, 9qm, 9qs, shown in SEQ ID NOs:13, 15, 17, 19, 21, 23, and 25) bind to and modulate potassium channels containing a Kv4.2 or Kv4.3 subunit and contain calcium binding EF-hand domains. Because of mutations in these PCIP genes, defects in the expression of these calcium-binding PCIP proteins themselves, or defects in the interaction between these PCIPs and Kv4.2 or Kv4.3 channels, might be expected to lead to decreases in KV4.3 or Kv4.3(I_m) currents in the myocardium, therapeutic agents that alter PCIP expression or modulate the interaction between these PCIPs and Kv4.2 or Kv4.3 may be extremely valuable agents to slow or prevent the progression of disease from hypertrophy to heart failure.

As used herein, a "potassium channel associated disorder" includes a disorder, disease or condition which is characterized by a misregulation of a potassium channel mediated activity. Potassium channel associated disorders can detrimentally affect conveyance of sensory impulses from the periphery to the brain and/or conductance of motor impulses from the brain to the periphery; integration of reflexes; interpretation of sensory impulses; and emotional, intellectual (e.g., learning and memory), or motor

processes. Potassium channel associated disorders can further detrimentally affect electrical impulses that stimulate the cardiac muscle fibers to contract. Examples of potassium channel associated disorders include nervous system related disorders, as well as cardiovascular disorders.

- 5 As used herein, a “nervous system related disorder” includes a disorder, disease or condition which affects the nervous system. Examples of potassium channel associated disorders and nervous system related disorders include cognitive disorders, e.g., memory and learning disorders, such as amnesia, apraxia, agnosia, amnestic dysnomia, amnestic spatial disorientation, Kluver-Bucy syndrome, Alzheimer's related 10 memory loss (Eglen R.M. (1996) *Pharmacol. and Toxicol.* 78(2):59-68; Perry E.K. (1995) *Brain and Cognition* 28(3):240-58) and learning disability; disorders affecting consciousness, e.g., visual hallucinations, perceptual disturbances, or delerium associated with Lewy body dementia; schizto-effective disorders (Dean B. (1996) *Mol. Psychiatry* 1(1):54-8), schizophrenia with mood swings (Bymaster F.P. (1997) *J. Clin. Psychiatry* 58 (suppl.10):28-36; Yeomans J.S. (1995) *Neuropharmacol.* 12(1):3-16; Reimann D. (1994) *J. Psychiatric Res.* 28(3):195-210), depressive illness (primary or secondary); affective disorders (Janowsky D.S. (1994) *Am. J. Med. Genetics* 54(4):335-44); sleep disorders (Kimura F. (1997) *J. Neurophysiol.* 77(2):709-16), e.g., REM sleep abnormalities in patients suffering from, for example, depression (Reimann D. (1994) *J. Psychosomatic Res.* 38 Suppl. 1:15-25; Bourgin P. (1995) *Neuroreport* 6(3): 532-6), paradoxical sleep abnormalities (Sakai K. (1997) *Eur. J. Neuroscience* 9(3):415-23), sleep-wakefulness, and body temperature or respiratory depression abnormalities during sleep (Shuman S.L. (1995) *Am. J. Physiol.* 269(2 Pt 2):R308-17; Mallick B.N. (1997) *Brain Res.* 750(1-2):311-7). Other examples of nervous system related disorders include 20 disorders affecting pain generation mechanisms, e.g., pain related to irritable bowel syndrome (Mitch C.H. (1997) *J. Med. Chem.* 40(4):538-46; Shannon H.E. (1997) *J. Pharmac. and Exp. Therapeutics* 281(2):884-94; Bouaziz H. (1995) *Anesthesia and Analgesia* 80(6):1140-4; or Guimaraes A.P. (1994) *Brain Res.* 647(2):220-30) or chest pain; movement disorders (Monassi C.R. (1997) *Physiol. and Behav.* 62(1):53-9), e.g., 25 Parkinson's disease related movement disorders (Finn M. (1997) *Pharmacol. Biochem. & Behavior* 57(1-2):243-9; Mayorga A.J. (1997) *Pharmacol. Biochem. & Behavior*

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- 56(2):273-9); eating disorders, e.g., insulin hypersecretion related obesity (Maccario M. (1997) *J. Endocrinol. Invest.* 20(1):8-12; Premawardhana L.D. (1994) *Clin. Endocrinol.* 40(5): 617-21); drinking disorders, e.g., diabetic polydipsia (Murzi E. (1997) *Brain Res.* 752(1-2):184-8; Yang X. (1994) *Pharmacol. Biochem. & Behavior* 49(1):1-6);
- 5 neurodegenerative disorders, e.g., Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, epileptic syndromes, and Jakob-Creutzfeldt disease; psychiatric disorders, e.g., depression, schizophrenic disorders, Korsakoff's psychosis,
- 10 mania, anxiety disorders, bipolar affective disorders, or phobic disorders; neurological disorders, e.g., migraine; spinal cord injury; stroke; and head trauma.

As used herein, "epilepsy" includes a common neurological disorder caused by disturbances in the normal electrical functions of the brain. In normal brain function millions of tiny electrical charges pass from nerve cells in the brain to all parts of the body. In patients with epilepsy, this normal pattern is interrupted by sudden and unusually intense bursts of electrical energy, which may briefly affect a person's consciousness, bodily movements, or sensations. These physical changes are called epileptic seizures. There are two categories of seizures: partial seizures, which occur in one area of the brain, and generalized seizures, which affect nerve cells throughout the brain. Epilepsy may result from a brain injury before, during, or after birth; head trauma; poor nutrition; some infectious diseases; brain tumors; and some poisons. However, in many cases the cause is unknown. Attacks of epilepsy may be preceded by a feeling of unease or sensory discomfort called an aura, which indicates the beginning of the seizure. Signs of an impending epileptic seizure, which vary among patients, may include visual phenomena such as flickering lights or "sunbursts." Recently, a genetic linkage for epilepsy has been found on chromosome 10q, near marker D10S192: 10q22-q24 (Ottman et al. (1995) *Nature Genetics* 10:56-60). The many forms of epilepsy include: grand mal, Jacksonian, myoclonic progressive familial, petit mal, Lennox-Gastaut syndrome, febrile seizures, psycho-motor, and temporal lobe. The observations described herein are particularly useful in developing treatments for partial epilepsy.

As used herein, "ataxia" includes a common neurological disorder caused by disturbances in the normal electrical functions of the brain. Spinocerebellar ataxia type 1 (SCA1) is an autosomal dominant disorder which is genetically linked to the short arm of chromosome 6 based on linkage to the human major histocompatibility complex (HLA). See, for example, H. Yakura *et al.* (1974) *N. Engl. J. Med.*, 291, 154-155; and J. F. Jackson *et al.* (1977) *N. Engl. J. Med.* 296, 1138-1141. SCA1 has been shown to be tightly linked to the marker D6S89 on the short arm of chromosome 6, telomeric to HLA. See, for example, L. P. W. Ranum *et al.*, *Am. J. Hum. Genet.*, 49, 31-41 (1991); and H. Y. Zoghbi *et al.*, *Am. J. Hum. Genet.*, 49, 23-30 (1991). The observations described herein are particularly useful in developing treatments for infantile onset spinocerebellar ataxia (IOSCA).

As used herein, a "cardiovascular disorder" includes a disorder affecting the cardiovascular system, *e.g.*, the heart. Examples of cardiovascular disorders include arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia. In a preferred embodiment, the cardiovascular disorder is associated with an abnormal I_{to} current.

Some members of a PCIP family may also have common structural characteristics, such as a common structural domain or motif or a sufficient amino acid 25 or nucleotide sequence homology as defined herein. Such PCIP family members can be naturally or non-naturally occurring and can be from either the same or different species. For example, a PCIP family can contain a first protein of human origin, as well as other, distinct proteins of human origin or alternatively, can contain homologues of non-human origin.

30 For example, members of a PCIP family which have common structural characteristics, may comprise at least one "calcium binding domain". As used herein,

the term "calcium binding domain" includes an amino acid domain, *e.g.*, an EF hand (Bainbridge K.G. *et al.* (1992) *TINS* 15(8): 303-308), which is involved in calcium binding. Preferably, a calcium binding domain has a sequence, which is substantially identical to the consensus sequence:

5

EO**OO**ODKDGDG•Q***EF**OO. (SEQ ID NO:41).

- O can be I, L, V or M, and "*" indicates a position with no strongly preferred residue. Each residue listed is present in more than 25% of sequences, and those underlined are
- 10 present in more than 80% of sequences. Amino acid residues 126-154 and 174-202 of the human 1v protein, amino acid residues 126-154 and 174-202 of the rat 1v protein, amino acid residues 137-165 and 185-213 of the rat 1vl protein, amino acid residues 142-170 of the rat 1vn protein, amino acid residues 126-154 and 174-202 of the mouse 1v protein, amino acid residues 137-165 and 185-213 of the mouse 1vl protein, amino
- 15 acid residues 144-172, 180-208, and 228-256 of the human 9q1 protein, amino acid residues 126-154, 162-190, and 210-238 of the human 9qm protein, amino acid residues 94-122, 130-158, and 178-206 of the human 9qs protein, amino acid residues 126-154, 162-190, and 210-238 of the rat 9qm protein, amino acid residues 131-159, 167-195, and 215-243 of the rat 9ql protein, amino acid residues 126-154, 162-190, and 210-238
- 20 of the rat 9qc protein, amino acid residues 99-127, 135-163, and 183-211 of the rat 8t protein, amino acid residues 144-172, 180-208, and 228-256 of the mouse 9ql protein, amino acid residues 94-122, 130-158, and 178-206 of the monkey 9qs protein, amino acid residues 94-122, 130-158, and 178-206 of the human p19 protein, amino acid residues 19-47 and 67-95 of the rat p19 protein, and amino acid residues 130-158, 166-
- 25 194, and 214-242 of the mouse p19 protein comprise calcium binding domains (EF hands) (see Figure 21). Amino acid residues 116-127 and 152-163 of the monkey KChIP4a and KChIP4b proteins comprise calcium binding domains.

- In another embodiment, the isolated PCIP proteins of the present invention are identified based on the presence of at least one conserved carboxyl-terminal domain
- 30 which includes an amino acid sequence of about 100-200 amino acid residues in length, preferably 150-200 amino acid residues in length, and more preferably 185 amino acid

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residues in length, and which includes three EF hands. PCIP proteins of the present invention preferably contain a carboxyl-terminal domain which is at least about 70%, 71%, 74%, 75%, 76%, 80%, or more identical to the carboxyl terminal 185 amino acid residues of rat 1v, rat 9q, or mouse p19 (see Figures 21, 25, and 41).

- 5 Members of the PCIP family which also have common structural characteristics are listed in Table I and described below. The invention provides full length human, mouse, and rat 1v cDNA clones, full length mouse and rat cDNA clones of 1v splice variant 1vl, a partial rat cDNA clone of 1v splice variant 1vn, and the proteins encoded by these cDNAs. The invention further provides full length human and mouse and
10 partial rat 9ql cDNA clones, full length human and rat cDNA clones of 9ql splice variant 9qm, full length human and monkey cDNA clones of 9ql splice variant 9qs, a full length rat cDNA clone of 9ql splice variant 9qc, a partial rat cDNA clone of 9ql splice variant 8t, and the proteins encoded by these cDNAs. The invention also provides full length mouse and human and partial rat p19 cDNA clones and the proteins encoded by these
15 cDNAs. A full length human cDNA clone of p19 is provided, and a partial clone p193, representing the 3' end of the human p19 cDNA. In addition, the invention provides a partial human W28559 cDNA clone and the protein encoded by this cDNA. The invention further provides a full length monkey clone, KChIP4a, and a corresponding full length splice variant, KChIP4b and the proteins encoded by these cDNAs.
- 20 Other members of the PCIP family, *e.g.*, members of the PCIP family which do not have common structural characteristics, are listed in Table II and are described below. The present invention provides a full length human and a partial length rat 33b07 clone and the proteins encoded by these cDNAs. The present invention further provides partial length rat 1p clone and the protein encoded by this cDNA. In addition,
25 the present invention provides a partial length rat 7s clone and the protein encoded by this cDNA.

- The present invention further provides PCIP family members which represent previously identified cDNAs (29x, 25r, 5p, 7q, and 19r). These previously identified cDNAs are identified herein as PCIP family members, *i.e.*, as molecules which have a
30 PCIP activity, as described herein. Accordingly, the present invention provides methods for using these previously identified cDNAs, *e.g.*, methods for using these cDNAs in the

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screening assays, the diagnostic assays, the prognostic assays, and the methods of treatment described herein.

The PCIP molecules of the present invention were initially identified based on their ability, as determined using yeast two-hybrid assays (described in detail in 5 Example 1), to interact with the amino-terminal 180 amino acids of rat Kv4.3 subunit. Further binding studies with other potassium subunits were performed to demonstrate specificity of the PCIP for Kv4.3 and Kv4.2. *In situ* localization, immuno-histochemical methods, co-immunoprecipitation and patch clamping methods were then used to clearly demonstrate that the PCIPs of the present invention interact with and modulate the 10 activity of potassium channels, particularly those comprising a 4.3 or 4.2 subunit.

Several novel human, mouse, monkey, and rat PCIP family members have been identified, referred to herein as 1v, 9q, p19, W28559, KChIP4, 33b07, 1p, and rat 7s 15 proteins and nucleic acid molecules. The human, rat, and mouse cDNAs encoding the 1v polypeptide are represented by SEQ ID NOs:1, 3, and 5, and shown in Figures 1, 2, and 3, respectively. In the brain, 1v mRNA is highly expressed in neocortical and hippocampal interneurons, in the thalamic reticular nucleus and medial habenula, in basal forebrain and striatal cholinergic neurons, in the superior colliculus, and in cerebellar granule cells. The 1v polypeptide is highly expressed in the somata, dendrites, axons and axon terminals of cells that express 1v mRNA. Splice variants of 20 the 1v gene have been identified in rat and mouse and are represented by SEQ ID NOs: 7, 9, and 11 and shown in Figures 4, 5, and 6, respectively. 1v polypeptide interacts with potassium channels comprising Kv4.3 or kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot, the 1v transcripts (mRNA) are expressed predominantly in the brain.

25 The 8t cDNA (SEQ ID NO: 29) encodes a polypeptide having a molecular weight of approximately 26 kD corresponding to SEQ ID NO:30 (see Figure 15). The 8t polypeptide interacts with potassium channel comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot and *in situ* data, the 8t mRNA is expressed predominantly in the heart and the brain. The 8t cDNA is a splice variant of 30 9q.

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Human, rat, monkey, and mouse 9q cDNA were also isolated. Splice variants include human 9ql (SEQ ID NO:13; Figure 7) rat 9ql (SEQ ID NO:15; Figure 8), mouse 9ql (SEQ ID NO:17; Figure 9), human 9qm (SEQ ID NO:19; Figure 10), rat 9qm (SEQ ID NO:21; Figure 11), human 9qs (SEQ ID NO:23; Figure 12), monkey 9qs (SEQ ID NO:25; Figure 13), and rat 9qc (SEQ ID NO:27; Figure 14). The genomic DNA sequence of 9q has also been determined. Exon 1 and its flanking intron sequences (SEQ ID NO:46) are shown in Figure 22A. Exons 2-11 and the flanking intron sequences (SEQ ID NO:47) are shown in Figure 22B. 9q polypeptides interact with potassium channels comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot and *in situ* data, the 9q proteins are expressed predominantly in the heart and the brain. In the brain, 9q mRNA is highly expressed in the neostriatum, hippocampal formation, neocortical pyramidal cells and interneurons, and in the thalamus, superior colliculus, and cerebellum.

Human, rat, and mouse P19 cDNA was also isolated. Human P19 is shown in SEQ ID NO:31 and Figure 16; and in SEQ ID NO:39 and Figure 20 (the 3' sequence). Rat P19 is shown in SEQ ID NO:33 and Figure 17, and mouse P19 is shown in SEQ ID NO:35 and Figure 18. P19 polypeptides interact with potassium channels comprising Kv4.3 or Kv4.2 subunits, but not with Kv1.1 subunits. As determined by Northern blot analysis, the P19 transcripts (mRNA) are expressed predominantly in the brain.

A partial human paralog of the PCIP molecules was also identified. This paralog is referred to herein as W28559 and is shown in SEQ ID NO:37 and Figure 19.

Monkey KChIP4a and its splice variants KChIP4b, KChIP4c, and KChIP4d were also identified. Monkey KChIP4a is shown in SEQ ID NO:48 and Figure 23. Monkey KChIP4b is shown in SEQ ID NO:50 and Figure 24. Monkey KChIP4c is shown in SEQ ID NO:69 and Figure 35. Monkey KChIP4d is shown in SEQ ID NO:71 and Figure 36.

The nucleotide sequence of the full length rat 33b07 cDNA and the predicted amino acid sequence of the rat 33b07 polypeptide are shown in Figure 26 and in SEQ ID NOS:52 and 53, respectively. The rat 33b07 cDNA encodes a protein having a molecular weight of approximately 44.7 kD and which is 407 amino acid residues in

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length. Rat 33b07 binds rKv4.3N and rKv4.2N with slight preference for rKv4.2N in yeast 2-hybrid assays.

The nucleotide sequence of the full length human 33b07 cDNA and the predicted amino acid sequence of the human 33b07 polypeptide are shown in Figure 27 and in
5 SEQ ID NOs:54 and 55, respectively.

The nucleotide sequence of the partial length rat 1p cDNA and the predicted amino acid sequence of the rat 1p polypeptide are shown in Figure 28 and in SEQ ID NOs:56 and 57, respectively. The rat 1p cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 267 amino acid residues in length. Rat
10 1p binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast two-hybrid assays.

The nucleotide sequence of the partial length rat 7s cDNA and the predicted amino acid sequence of the rat 7s polypeptide are shown in Figure 29 and in SEQ ID NOs:58 and 59, respectively. The rat 7s cDNA encodes a protein having a molecular
15 weight of approximately 28.6 kD and which is 270 amino acid residues in length. Rat 7s binds rKv4.3N and rKv4.2N with preference for rKv4.3N in yeast two-hybrid assays.

The sequences of the present invention are summarized below, in Tables I and II.

20 Table I

Novel Polynucleotides and Polypeptides of the Present Invention (full length except where noted)

PCIP	Nucleic Acid Molecule Form	Source	SEQ ID NO: DNA	SEQ ID NO: PROTEIN	ATCC
Iv or KChIP1	Iv	human (225-875)*	1	2	98994
	Iv	rat (210-860)	3	4	98946

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	1v	mouse (477-1127)	5	6	98945
	1vl	rat (31-714)	7	8	98942
	1vl	mouse (77-760)	9	10	98943
	1vn (partial)	rat (345-955)	11	12	98944
9q or KChIP2	Genomic DNA sequence (Exon 1 and flanking intron sequences)	human	46		
	Genomic DNA sequence (Exons 2-11 and flanking intron sequences)	human	47		
	9ql	human (207-1019)	13	14	98993 98991
	9ql (partial)	rat (2-775)	15	16	98948
	9ql	mouse (181 -993)	17	18	98937
	9qm	human (207-965)	19	20	98993 98991
	9qm	rat (214-972)	21	22	98941

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	9qs	human (207-869)	23	24	98951
	9qs	monkey (133-795)	25	26	98950
	9qc	rat (208-966)	27	28	98947
	8t (partial)	rat (1-678)	29	30	98939
p19 or KChIP3	p19	Human (1-771)	31	32	PTA-316
	p19 (partial)	rat (1-330)	33	34	98936
	p19	mouse (49-819)	35	36	98940
	p193 (partial)	Human (2-127)	39	40	98949
W28559	W28559 (partial)	human (1-339)	37	38	
KChIP4	KChIP4a	Monkey (265-966)	48	49	
	KChIP4b C-terminal splice variant	Monkey (265-966)	50	51	
	KChIP4c splice variant	Monkey (122-811)	69	70	
	KChIP4d splice variant	Monkey (64-816)	71	72	

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* The coordinates of the coding sequence are shown in parenthesis. The first column indicates the PCIPs which were identified and column 2 indicates the various nucleic acid forms identified for each PCIP.

5 Table II

Polynucleotides and Polypeptides of the Present Invention (full length except where noted)

PCIP	Nucleic Acid Molecule Form	Source	SEQ ID NO: DNA	SEQ ID NO: PROTEIN	ATCC
33b07 Novel	33b07	Human (88-1332)	52	53	PTA-316
	33b07	Rat (85-1308)	54	55	
1p Novel	1p (partial)	Rat (1-804)	56	57	
7s Novel	7s (partial)	Rat (1-813)	58	59	
29x	29x	Rat (433-1071)	60	61	
	25r splice variant of 29x	Rat (130-768)	62		
5p	5p	Rat (52-339)	63	64	
7q	7q	Rat (1-639)	65	66	
19r	19r	Rat (1-816)	67	68	

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* The coordinates of the coding sequence are shown in parenthesis. The first column indicates the four families of PCIPs which were identified and column 2 indicates the various nucleic acid forms identified for each family. Novel molecules are also indicated.

- 5 Plasmids containing the nucleotide sequences encoding human, rat and monkey PCIPs were deposited with American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, VA 20110-2209, on November 17, 1998, and assigned the Accession Numbers described above. These deposits will be maintained under the terms of the Budapest Treaty on the International Recognition of the Deposit of
10 Microorganisms for the Purposes of Patent Procedure. These deposits were made merely as a convenience for those of skill in the art and are not an admission that a deposit is required under 35 U.S.C. §112.

Clones containing cDNA molecules encoding human p19 (clone EphP19) and human 33b07 (clone Eph33b07) were deposited with American Type Culture Collection
15 (Manassas, VA) on July 8, 1998 as Accession Number PTA-316, as part of a composite deposit representing a mixture of two strains, each carrying one recombinant plasmid harboring a particular cDNA clone. (The ATCC strain designation for the mixture of hP19 and h33b07 is EphP19h33b07mix).

To distinguish the strains and isolate a strain harboring a particular cDNA clone,
20 an aliquot of the mixture can be streaked out to single colonies on LB plates supplemented with 100 ug/ml ampicillin, single colonies grown, and then plasmid DNA extracted using a standard minipreparation procedure. Next, a sample of the DNA minipreparation can be digested with NotI and the resultant products resolved on a 0.8% agarose gel using standard DNA electrophoresis conditions. The digest gives the
25 following band patterns: EphP19: 7 kb 9 (single band), Eph33b07: 5.8 kb (single band).

Various aspects of the invention are described in further detail in the following subsections:

I. Isolated Nucleic Acid Molecules

- One aspect of the invention pertains to isolated nucleic acid molecules that encode PCIP proteins or biologically active portions thereof, as well as nucleic acid fragments sufficient for use as hybridization probes to identify PCIP-encoding nucleic acid molecules (*e.g.*, PCIP mRNA) and fragments for use as PCR primers for the amplification or mutation of PCIP nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The
- 5 nucleic acid molecule can be single-stranded or double-stranded, but preferably is double-stranded DNA.
- 10

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid. Preferably, an "isolated" nucleic acid is free of sequences which naturally flank the nucleic acid (*i.e.*, sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated PCIP nucleic acid molecule can contain less than about 5 kb, 4kb, 3kb, 2kb, 1 kb, 0.5 kb or 0.1 kb of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover, the

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20 an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques, or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention, *e.g.*, a nucleic acid molecule having the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with

- ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion thereof, can be isolated using standard molecular biology techniques and the sequence information provided herein. Using all or portion of the nucleic acid
- 5 sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, as a hybridization probe, PCIP nucleic acid molecules can be isolated using standard
- 10 hybridization and cloning techniques (e.g., as described in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).
- 15 Moreover, a nucleic acid molecule encompassing all or a portion of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 can be isolated by the polymerase chain reaction (PCR) using synthetic oligonucleotide primers designed based upon the
- 20 sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ

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ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the
5 nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994.

A nucleic acid of the invention can be amplified using cDNA, mRNA or alternatively, genomic DNA, as a template and appropriate oligonucleotide primers
10 according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, oligonucleotides corresponding to PCIP nucleotide sequences can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In a preferred embodiment, an isolated nucleic acid molecule of the invention
15 comprises the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion of any of these nucleotide sequences.

25 In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which is a complement of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID

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- NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or
- 5 98994, or a portion of any of these nucleotide sequences. A nucleic acid molecule which is complementary to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID
- 10 NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, is one which is sufficiently complementary to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:9, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950,
- 15 98951, 98991, 98993, or 98994, such that it can hybridize to the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID
- 20 NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, thereby
- 25 forming a stable duplex.

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In still another preferred embodiment, an isolated nucleic acid molecule of the present invention comprises a nucleotide sequence which is at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98% or more identical to the entire length of the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ

- 5 ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID
NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID
NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID
NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID
NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID
10 NO:69, or SEQ ID NO:71, or the entire length of the nucleotide sequence of the DNA
insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938,
98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949,
98950, 98951, 98991, 98993, or 98994, or a portion of any of these nucleotide
sequences.

15 Moreover, the nucleic acid molecule of the invention can comprise only a portion
of the nucleic acid sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID
NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17,
SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ
ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID
20 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID
NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID
NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with
ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942,
98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or
25 98994, for example a fragment which can be used as a probe or primer or a fragment
encoding a biologically active portion of a PCIP protein. The nucleotide sequence
determined from the cloning of the PCIP gene allows for the generation of probes and
primers designed for use in identifying and/or cloning other PCIP family members, as
well as PCIP homologues from other species.

30 The probe/primer typically comprises substantially purified oligonucleotide. The
oligonucleotide typically comprises a region of nucleotide sequence that hybridizes

- under stringent conditions to at least about 12 or 15, preferably about 20 or 25, more preferably about 30, 35, 40, 45, 50, 55, 60, 65, or 75 consecutive nucleotides of a sense sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ
5 ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as
10 Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, of an anti-sense sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID
15 NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or of a naturally occurring allelic variant or mutant of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID
25 NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In an exemplary embodiment, a nucleic acid molecule of the present invention comprises a nucleotide sequence which is 350-400,

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- 400-450, 450-500, 500-550, 550-600, 600-650, 650-700, 700-750, 750-800, 800-850,
850-900, 949, 950-1000, or more nucleotides in length and hybridizes under stringent
hybridization conditions to a nucleic acid molecule of SEQ ID NO:1, SEQ ID NO:3
SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID
5 NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID
NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID
NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID
NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID
NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA
10 insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938,
98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949,
98950, 98951, 98991, 98993, or 98994.

Probes based on the PCIP nucleotide sequences can be used to detect transcripts
or genomic sequences encoding the same or homologous proteins. In preferred
15 embodiments, the probe further comprises a label group attached thereto, e.g., the label
group can be a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-
factor. Such probes can be used as a part of a diagnostic test kit for identifying cells or
tissue which misexpress a PCIP protein, such as by measuring a level of a PCIP-
encoding nucleic acid in a sample of cells from a subject e.g., detecting PCIP mRNA
20 levels or determining whether a genomic PCIP gene has been mutated or deleted.

A nucleic acid fragment encoding a "biologically active portion of a PCIP
protein" can be prepared by isolating a portion of the nucleotide sequence of SEQ ID
NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11,
SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ
25 ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID
NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID
NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID
NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence
of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936,
30 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947,
98948, 98949, 98950, 98951, 98991, 98993, or 98994, which encodes a polypeptide

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having a PCIP biological activity (the biological activities of the PCIP proteins are described herein), expressing the encoded portion of the PCIP protein (*e.g.*, by recombinant expression *in vitro*) and assessing the activity of the encoded portion of the PCIP protein.

- 5 The invention further encompasses nucleic acid molecules that differ from the nucleotide sequence shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, due to degeneracy of the 10 genetic code and thus encode the same PCIP proteins as those encoded by the nucleotide sequence shown in SSEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another embodiment, an isolated nucleic acid molecule of the invention has a 15 nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another embodiment, an isolated nucleic acid molecule of the invention has a 20 nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another embodiment, an isolated nucleic acid molecule of the invention has a 25 nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In another embodiment, an isolated nucleic acid molecule of the invention has a 30 nucleotide sequence encoding a protein having an amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994.

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NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

- In addition to the PCIP nucleotide sequences shown in SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, 5 SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA 10 insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, it will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequences of the PCIP proteins may exist within a population (*e.g.*, the human population). Such 15 genetic polymorphism in the PCIP genes may exist among individuals within a population due to natural allelic variation. As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules which include an open reading frame encoding a PCIP protein, preferably a mammalian PCIP protein, and can further include non-coding regulatory sequences, and introns.
- 20 Allelic variants of human PCIP include both functional and non-functional PCIP proteins. Functional allelic variants are naturally occurring amino acid sequence variants of the human PCIP protein that maintain the ability to bind a PCIP ligand and/or modulate any of the PCIP activities described herein. Functional allelic variants will typically contain only conservative substitution of one or more amino acids of SEQ ID 25 NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID 30 NO:70, or SEQ ID NO:72 or substitution, deletion or insertion of non-critical residues in non-critical regions of the protein.

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- Non-functional allelic variants are naturally occurring amino acid sequence variants of the human PCIP protein that do not have the ability to either bind a PCIP ligand and/or modulate any of the PCIP activities described herein. Non-functional allelic variants will typically contain a non-conservative substitution, a deletion, or
- 5 insertion or premature truncation of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID
- 10 NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or a substitution, insertion or deletion in critical residues or critical regions.

The present invention further provides non-human orthologues of the human PCIP protein. Orthologues of the human PCIP protein are proteins that are isolated from non-human organisms and possess the same PCIP ligand binding and/or modulation of

15 potassium channel mediated activities of the human PCIP protein. Orthologues of the human PCIP protein can readily be identified as comprising an amino acid sequence that is substantially identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID

20 NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

Moreover, nucleic acid molecules encoding other PCIP family members and, thus, which have a nucleotide sequence which differs from the PCIP sequences of SEQ

25 ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID

30 NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936,

- 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 are intended to be within the scope of the invention. For example, another PCIP cDNA can be identified based on the nucleotide sequence of human PCIP. Moreover, nucleic acid molecules encoding PCIP
- 5 proteins from different species, and thus which have a nucleotide sequence which differs from the PCIP sequences of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID
- 10 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or
- 15 98994 are intended to be within the scope of the invention. For example, a mouse PCIP cDNA can be identified based on the nucleotide sequence of a human PCIP.

Nucleic acid molecules corresponding to natural allelic variants and homologues of the PCIP cDNAs of the invention can be isolated based on their homology to the PCIP nucleic acids disclosed herein using the cDNAs disclosed herein, or a portion 20 thereof, as a hybridization probe according to standard hybridization techniques under stringent hybridization conditions.

Accordingly, in another embodiment, an isolated nucleic acid molecule of the invention is at least 15, 20, 25, 30 or more nucleotides in length and hybridizes under stringent conditions to the nucleic acid molecule comprising the nucleotide sequence of

25 SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as

- Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. In other embodiment, the nucleic acid is at least 30, 50, 100, 150, 200, 250, 300, 307, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 949, or 950 nucleotides in length.
- 5 used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% identical to each other typically remain hybridized to each other. Preferably, the conditions are such that sequences at least about 70%, more preferably at least about 80%, even more preferably at least about 85% or 90% identical to each other typically 10 remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found in *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989), 6.3.1-6.3.6. A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2 X SSC, 0.1% SDS at 50°C, preferably at 55°C, 15 and more preferably at 60°C or 65°C. Preferably, an isolated nucleic acid molecule of the invention that hybridizes under stringent conditions to the sequence of SEQ ID NO:1 corresponds to a naturally-occurring nucleic acid molecule. As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in nature (e.g., encodes a natural protein).
- 20 In addition to naturally-occurring allelic variants of the PCIP sequences that may exist in the population, the skilled artisan will further appreciate that changes can be introduced by mutation into the nucleotide sequences of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID 25 NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 30 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949,

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- 98950, 98951, 98991, 98993, or 98994, thereby leading to changes in the amino acid sequence of the encoded PCIP proteins, without altering the functional ability of the PCIP proteins. For example, nucleotide substitutions leading to amino acid substitutions at "non-essential" amino acid residues can be made in the sequence of SEQ ID NO:1,
- 5 SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence of PCIP (e.g., the sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72) without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are conserved among the PCIP proteins of the present invention, are predicted to be particularly unamenable to alteration. Furthermore, additional amino acid residues that are conserved between the PCIP proteins of the present invention and other members of the PCIP family of proteins are not likely to be amenable to alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding PCIP proteins that contain changes in amino acid residues that are not essential for activity. Such PCIP proteins differ in amino acid sequence from SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID

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- NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, yet retain biological activity. In one embodiment, the
- 5 isolated nucleic acid molecule comprises a nucleotide sequence encoding a protein, wherein the protein comprises an amino acid sequence at least about 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or more identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ
- 10 ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

An isolated nucleic acid molecule encoding a PCIP protein homologous to the protein of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 can be created by introducing one or more nucleotide substitutions, additions or deletions into the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, such that one or more amino acid substitutions, additions or deletions are introduced into the encoded protein. Mutations

can be introduced into SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID 5 NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 10 98994 by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been 15 defined in the art. These families include amino acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., 20 threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Thus, a predicted nonessential amino acid residue in a PCIP protein is preferably replaced with another amino acid residue from the same side chain family. Alternatively, in another embodiment, mutations can be introduced randomly along all or part of a PCIP coding sequence, such as by saturation mutagenesis, and the 25 resultant mutants can be screened for PCIP biological activity to identify mutants that retain activity. Following mutagenesis of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID 30 NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID

NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, the encoded protein can be expressed recombinantly and the
5 activity of the protein can be determined.

In a preferred embodiment, a mutant PCIP protein can be assayed for the ability to (1) interact with (*e.g.*, bind to) a potassium channel protein or portion thereof; (2) regulate the phosphorylation state of a potassium channel protein or portion thereof; (3) associate with (*e.g.*, bind) calcium and, for example, act as a calcium dependent kinase,
10 *e.g.*, phosphorylate a potassium channel in a calcium-dependent manner; (4) associate with (*e.g.*, bind) calcium and, for example, act as a calcium dependent transcription factor; (5) modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) modulate the release of neurotransmitters; (7) modulate membrane excitability; (8) influence the resting
15 potential of membranes; (9) modulate wave forms and frequencies of action potentials; and (10) modulate thresholds of excitation.

In addition to the nucleic acid molecules encoding PCIP proteins described above, another aspect of the invention pertains to isolated nucleic acid molecules which are antisense thereto. An "antisense" nucleic acid comprises a nucleotide sequence
20 which is complementary to a "sense" nucleic acid encoding a protein, *e.g.*, complementary to the coding strand of a double-stranded cDNA molecule or complementary to an mRNA sequence. Accordingly, an antisense nucleic acid can hydrogen bond to a sense nucleic acid. The antisense nucleic acid can be complementary to an entire PCIP coding strand, or to only a portion thereof. In one
25 embodiment, an antisense nucleic acid molecule is antisense to a "coding region" of the coding strand of a nucleotide sequence encoding PCIP. The term "coding region" refers to the region of the nucleotide sequence comprising codons which are translated into amino acid residues. In another embodiment, the antisense nucleic acid molecule is antisense to a "noncoding region" of the coding strand of a nucleotide sequence
30 encoding PCIP. The term "noncoding region" refers to 5' and 3' sequences which flank

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the coding region that are not translated into amino acids (*i.e.*, also referred to as 5' and 3' untranslated regions).

- Given the coding strand sequences encoding PCIP disclosed herein, antisense nucleic acids of the invention can be designed according to the rules of Watson and Crick base pairing. The antisense nucleic acid molecule can be complementary to the entire coding region of PCIP mRNA, but more preferably is an oligonucleotide which is antisense to only a portion of the coding or noncoding region of PCIP mRNA. For example, the antisense oligonucleotide can be complementary to the region surrounding the translation start site of PCIP mRNA. An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50 nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5- oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a

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nucleic acid has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

- The antisense nucleic acid molecules of the invention are typically administered
- 5 to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a PCIP protein to thereby inhibit expression of the protein, *e.g.*, by inhibiting transcription and/or translation. The hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through
 - 10 specific interactions in the major groove of the double helix. An example of a route of administration of antisense nucleic acid molecules of the invention include direct injection at a tissue site. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to
 - 15 receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is
 - 20 placed under the control of a strong pol II or pol III promoter are preferred.

- In yet another embodiment, the antisense nucleic acid molecule of the invention is an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual β -units, the strands run parallel to each other (Gaultier *et al.* (1987) *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-o-methylribonucleotide (Inoue *et al.* (1987) *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.* (1987) *FEBS Lett.* 215:327-330).

- In still another embodiment, an antisense nucleic acid of the invention is a ribozyme. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes

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- (described in Haselhoff and Gerlach (1988) *Nature* 334:585-591)) can be used to catalytically cleave PCIP mRNA transcripts to thereby inhibit translation of PCIP mRNA. A ribozyme having specificity for a PCIP-encoding nucleic acid can be designed based upon the nucleotide sequence of a PCIP cDNA disclosed herein (*i.e.*,
- 5 SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID
- 10 NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the nucleotide sequence of the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994). For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the
- 15 nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved in a PCIP-encoding mRNA. See, *e.g.*, Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742. Alternatively, PCIP mRNA can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules. See, *e.g.*, Bartel, D. and Szostak, J.W. (1993) *Science* 261:1411-1418.
- 20 Alternatively, PCIP gene expression can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the PCIP (*e.g.*, the PCIP promoter and/or enhancers) to form triple helical structures that prevent transcription of the PCIP gene in target cells. See generally, Helene, C. (1991) *Anticancer Drug Des.* 6(6):569-84; Helene, C. *et al.* (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher, L.J. (1992) *Bioassays* 14(12):807-15.
- In yet another embodiment, the PCIP nucleic acid molecules of the present invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose phosphate backbone of the nucleic acid molecules can be modified to
- 30 generate peptide nucleic acids (see Hyrup B. *et al.* (1996) *Bioorganic & Medicinal Chemistry* 4 (1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs"

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refer to nucleic acid mimics, e.g., DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis 5 of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *et al.* Proc. Natl. Acad. Sci. 93: 14670-675.

PNAs of PCIP nucleic acid molecules can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for 10 sequence-specific modulation of gene expression by, for example, inducing transcription or translation arrest or inhibiting replication. PNAs of PCIP nucleic acid molecules can also be used in the analysis of single base pair mutations in a gene, (e.g., by PNA-directed PCR clamping); as 'artificial restriction enzymes' when used in combination with other enzymes, (e.g., S1 nucleases (Hyrup B. (1996) *supra*)); or as probes or 15 primers for DNA sequencing or hybridization (Hyrup B. *et al.* (1996) *supra*; Perry-O'Keefe *supra*).

In another embodiment, PNAs of PCIP can be modified, (e.g., to enhance their stability or cellular uptake), by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of 20 drug delivery known in the art. For example, PNA-DNA chimeras of PCIP nucleic acid molecules can be generated which may combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, (e.g., RNase H and DNA polymerases), to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of 25 appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and orientation (Hyrup B. (1996) *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup B. (1996) *supra* and Finn P.J. *et al.* (1996) *Nucleic Acids Res.* 24 (17): 3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and 30 modified nucleoside analogs, e.g., 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite, can be used as a between the PNA and the 5' end of DNA (Mag, M. *et*

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al. (1989) *Nucleic Acid Res.* 17: 5973-88). PNA monomers are then coupled in a stepwise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn P.J. et al. (1996) *supra*). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser, K.H. et al. (1975) 5 *Bioorganic Med. Chem. Lett.* 5: 1119-1124).

In other embodiments, the oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al. (1989) *Proc. Natl. Acad. Sci. US.* 86:6553-6556; Lemaitre et al. (1987) *Proc. Natl. Acad. Sci. USA* 84:648-652; 10 PCT Publication No. W088/09810) or the blood-brain barrier (see, e.g., PCT Publication No. W089/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (See, e.g., Krol et al. (1988) *Bio-Techniques* 6:958-976) or intercalating agents. (See, e.g., Zon (1988) *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, (e.g., a peptide, hybridization 15 triggered cross-linking agent, transport agent, or hybridization-triggered cleavage agent).

II. Isolated PCIP Proteins and Anti-PCIP Antibodies

One aspect of the invention pertains to isolated PCIP proteins, and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens 20 to raise anti-PCIP antibodies. In one embodiment, native PCIP proteins can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, PCIP proteins are produced by recombinant DNA techniques. Alternative to recombinant expression, a PCIP protein or polypeptide can be synthesized chemically using standard peptide synthesis techniques. 25 An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the PCIP protein is derived, or substantially free from chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of PCIP protein in which 30 the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. In one embodiment, the language "substantially free of

"cellular material" includes preparations of PCIP protein having less than about 30% (by dry weight) of non-PCIP protein (also referred to herein as a "contaminating protein"), more preferably less than about 20% of non-PCIP protein, still more preferably less than about 10% of non-PCIP protein, and most preferably less than about 5% non-PCIP

- 5 protein. When the PCIP protein or biologically active portion thereof is recombinantly produced, it is also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, more preferably less than about 10%, and most preferably less than about 5% of the volume of the protein preparation.

The language "substantially free of chemical precursors or other chemicals"

- 10 includes preparations of PCIP protein in which the protein is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of PCIP protein having less than about 30% (by dry weight) of chemical precursors or non-PCIP chemicals, more preferably less than about 20%
- 15 chemical precursors or non-PCIP chemicals, still more preferably less than about 10% chemical precursors or non-PCIP chemicals, and most preferably less than about 5% chemical precursors or non-PCIP chemicals.

As used herein, a "biologically active portion" of a PCIP protein includes a fragment of a PCIP protein which participates in an interaction between a PCIP

- 20 molecule and a non-PCIP molecule. Biologically active portions of a PCIP protein include peptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the PCIP protein, *e.g.*, the amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, which include less amino acids than the full length PCIP proteins, and exhibit at least one activity of a PCIP protein. Typically,
- 25 biologically active portions comprise a domain or motif with at least one activity of the PCIP protein, *e.g.*, binding of a potassium channel subunit. A biologically active

portion of a PCIP protein can be a polypeptide which is, for example, 10, 25, 50, 100, 200, or more amino acids in length. Biologically active portions of a PCIP protein can be used as targets for developing agents which modulate a potassium channel mediated activity.

- 5 In one embodiment, a biologically active portion of a PCIP protein comprises at least one calcium binding domain.

It is to be understood that a preferred biologically active portion of a PCIP protein of the present invention may contain at least one of the above-identified structural domains. A more preferred biologically active portion of a PCIP protein may 10 contain at least two of the above-identified structural domains. Moreover, other biologically active portions, in which other regions of the protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of a native PCIP protein.

In a preferred embodiment, the PCIP protein has an amino acid sequence shown 15 in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID 20 NO:59, SEQ ID NO:70, or SEQ ID NO:72. In other embodiments, the PCIP protein is substantially homologous to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID 25 NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, and retains the functional activity of the protein of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID 30 NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID

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- NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72, yet differs in amino acid sequence due to natural allelic variation or mutagenesis, as described in detail in subsection I above. Accordingly, in another embodiment, the PCIP protein is a protein which comprises an amino acid sequence at least about 50%, 55%, 60%, 65%,
5 70%, 75%, 80%, 85%, 90%, 95%, 98% or more identical to SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID
10 NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72.

Isolated proteins of the present invention, preferably 1v, 9q, p19, W28559, KChIP4a, KChIP4b, 33b07, 1p, or 7s proteins, have an amino acid sequence sufficiently identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ
15 ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or are encoded by a nucleotide
20 sequence sufficiently identical to SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID
25 NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71. As used herein, the term "sufficiently identical" refers to a first amino acid or nucleotide sequence which contains a sufficient or minimum number of identical or equivalent (e.g., an amino acid residue which has a similar side chain) amino acid residues or nucleotides to a second amino acid or nucleotide sequence such that the first and second amino acid or nucleotide
30 sequences share common structural domains or motifs and/or a common functional activity. For example, amino acid or nucleotide sequences which share common structural domains

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- have at least 30%, 40%, or 50% identity, preferably 60% identity, more preferably 70%-80%, and even more preferably 90-95% identity across the amino acid sequences of the domains and contain at least one and preferably two structural domains or motifs, are defined herein as sufficiently identical. Furthermore, amino acid or nucleotide sequences
5 which share at least 30%, 40%, or 50%, preferably 60%, more preferably 70-80%, or 90-95% identity and share a common functional activity are defined herein as sufficiently identical.

Preferred proteins are PCIP proteins having at least one calcium binding domain and, preferably, a PCIP activity. Other preferred proteins are PCIP proteins having at least
10 one calcium binding domain, and are, preferably, encoded by a nucleic acid molecule having a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID
15 NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71.

To determine the percent identity of two amino acid sequences or of two nucleic
20 acid sequences, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in one or both of a first and a second amino acid or nucleic acid sequence for optimal alignment and non-homologous sequences can be disregarded for comparison purposes). In a preferred embodiment, the length of a reference sequence aligned for comparison purposes is at least 30%, preferably at least 40%, more
25 preferably at least 50%, even more preferably at least 60%, and even more preferably at least 70%, 80%, or 90% of the length of the reference sequence (*e.g.*, when aligning a second sequence to the PCIP amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID
30 NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID

- NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 having 177 amino acid residues, at least 80, preferably at least 100, more preferably at least 120, even more preferably at least 140, and even more preferably at least 150, 160 or 170 amino acid residues are aligned). The amino acid residues or
5 nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position (as used herein amino acid or nucleic acid "identity" is equivalent to amino acid or nucleic acid "homology"). The percent identity
10 between the two sequences is a function of the number of identical positions shared by the sequences, taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences.

The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm. In a preferred
15 embodiment, the percent identity between two amino acid sequences is determined using the Needleman and Wunsch (*J. Mol. Biol.* (48):444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package (available at <http://www.gcg.com>), using either a Blosum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6. In yet
20 another preferred embodiment, the percent identity between two nucleotide sequences is determined using the GAP program in the GCG software package (available at <http://www.gcg.com>), using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. In another embodiment, the percent identity between two amino acid or nucleotide sequences is determined using the
25 algorithm of E. Meyers and W. Miller (CABIOS, 4:11-17 (1989)) which has been incorporated into the ALIGN program (version 2.0 or 2.0U), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4.

The nucleic acid and protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example,
30 identify other family members or related sequences. Such searches can be performed using the NBLAST and XBLAST programs (version 2.0) of Altschul, *et al.* (1990) *J.*

- Mol. Biol.* 215:403-10. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to PCIP nucleic acid molecules of the invention. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3 to obtain 5 amino acid sequences homologous to PCIP protein molecules of the invention. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.*, (1997) *Nucleic Acids Res.* 25(17):3389-3402. When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, XBLAST and NBLAST) can be used. See <http://www.ncbi.nlm.nih.gov>.
- 10 The invention also provides PCIP chimeric or fusion proteins. As used herein, a PCIP "chimeric protein" or "fusion protein" comprises a PCIP polypeptide operatively linked to a non-PCIP polypeptide. An "PCIP polypeptide" refers to a polypeptide having an amino acid sequence corresponding to PCIP, whereas a "non-PCIP polypeptide" refers to a polypeptide having an amino acid sequence corresponding to a 15 protein which is not substantially homologous to the PCIP protein, *e.g.*, a protein which is different from the PCIP protein and which is derived from the same or a different organism. Within a PCIP fusion protein the PCIP polypeptide can correspond to all or a portion of a PCIP protein. In a preferred embodiment, a PCIP fusion protein comprises at least one biologically active portion of a PCIP protein. In another preferred 20 embodiment, a PCIP fusion protein comprises at least two biologically active portions of a PCIP protein. Within the fusion protein, the term "operatively linked" is intended to indicate that the PCIP polypeptide and the non-PCIP polypeptide are fused in-frame to each other. The non-PCIP polypeptide can be fused to the N-terminus or C-terminus of the PCIP polypeptide.
- 25 For example, in one embodiment, the fusion protein is a GST-PCIP fusion protein in which the PCIP sequences are fused to the C-terminus of the GST sequences. Such fusion proteins can facilitate the purification of recombinant PCIP.
- In another embodiment, the fusion protein is a PCIP protein containing a heterologous signal sequence at its N-terminus. In certain host cells (*e.g.*, mammalian 30 host cells), expression and/or secretion of PCIP can be increased through use of a heterologous signal sequence.

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- The PCIP fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject *in vivo*. The PCIP fusion proteins can be used to affect the bioavailability of a PCIP substrate. Use of PCIP fusion proteins may be useful therapeutically for the treatment of potassium channel associated disorders such as CNS disorders, *e.g.*, neurodegenerative disorders such as Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfieldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; and neurological disorders; *e.g.*, migraine. Use of PCIP fusion proteins may also be useful therapeutically for the treatment of potassium channel associated disorders such as cardiovascular disorders, *e.g.*, arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation or congestive heart failure.
- Moreover, the PCIP-fusion proteins of the invention can be used as immunogens to produce anti-PCIP antibodies in a subject, to purify PCIP ligands and in screening assays to identify molecules which inhibit the interaction of PCIP with a PCIP substrate.
- Preferably, a PCIP chimeric or fusion protein of the invention is produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques, for example by employing blunt-ended or stagger-ended termini for ligation, restriction enzyme digestion to provide for appropriate termini, filling-in of cohesive ends as appropriate, alkaline phosphatase treatment to avoid undesirable joining, and enzymatic ligation. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene

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- fragments which can subsequently be annealed and reamplified to generate a chimeric gene sequence (see, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (e.g., a GST polypeptide). A PCIP-
5 encoding nucleic acid can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the PCIP protein.

The present invention also pertains to variants of the PCIP proteins which function as either PCIP agonists (mimetics) or as PCIP antagonists. Variants of the PCIP proteins can be generated by mutagenesis, e.g., discrete point mutation or
10 truncation of a PCIP protein. An agonist of the PCIP proteins can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of a PCIP protein. An antagonist of a PCIP protein can inhibit one or more of the activities of the naturally occurring form of the PCIP protein by, for example, competitively modulating a potassium channel mediated activity of a PCIP protein. Thus, specific
15 biological effects can be elicited by treatment with a variant of limited function. In one embodiment, treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein has fewer side effects in a subject relative to treatment with the naturally occurring form of the PCIP protein.

In one embodiment, variants of a PCIP protein which function as either PCIP
20 agonists (mimetics) or as PCIP antagonists can be identified by screening combinatorial libraries of mutants, e.g., truncation mutants, of a PCIP protein for PCIP protein agonist or antagonist activity. In one embodiment, a variegated library of PCIP variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of PCIP variants can be produced by, for
25 example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential PCIP sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (e.g., for phage display) containing the set of PCIP sequences therein. There are a variety of methods which can be used to produce libraries of potential PCIP variants from a degenerate
30 oligonucleotide sequence. Chemical synthesis of a degenerate gene sequence can be performed in an automatic DNA synthesizer, and the synthetic gene then ligated into an

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appropriate expression vector. Use of a degenerate set of genes allows for the provision, in one mixture, of all of the sequences encoding the desired set of potential PCIP sequences. Methods for synthesizing degenerate oligonucleotides are known in the art (see, e.g., Narang, S.A. (1983) *Tetrahedron* 39:3; Itakura *et al.* (1984) *Annu. Rev. Biochem.* 53:323; Itakura *et al.* (1984) *Science* 198:1056; Ike *et al.* (1983) *Nucleic Acid Res.* 11:477.

In addition, libraries of fragments of a PCIP protein coding sequence can be used to generate a variegated population of PCIP fragments for screening and subsequent selection of variants of a PCIP protein. In one embodiment, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of a PCIP coding sequence with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes N-terminal, C-terminal and internal fragments of various sizes of the PCIP protein.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA libraries for gene products having a selected property. Such techniques are adaptable for rapid screening of the gene libraries generated by the combinatorial mutagenesis of PCIP proteins. The most widely used techniques, which are amenable to high throughput analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a new technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify PCIP variants (Arkin and Yourvan (1992) *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.* (1993) *Protein Engineering* 6(3):327-331).

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In one embodiment, cell based assays can be exploited to analyze a variegated PCIP library. For example, a library of expression vectors can be transfected into a cell line which ordinarily possesses a potassium channel mediated activity. The effect of the PCIP mutant on the potassium channel mediated activity can then be detected, *e.g.*, by

5 any of a number of enzymatic assays or by detecting the release of a neurotransmitter. Plasmid DNA can then be recovered from the cells which score for inhibition, or alternatively, potentiation of the potassium channel mediated activity, and the individual clones further characterized.

- An isolated PCIP protein, or a portion or fragment thereof, can be used as an
- 10 immunogen to generate antibodies that bind PCIP using standard techniques for polyclonal and monoclonal antibody preparation. A full-length PCIP protein can be used or, alternatively, the invention provides antigenic peptide fragments of PCIP for use as immunogens. The antigenic peptide of PCIP comprises at least 8 amino acid residues of the amino acid sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID
- 15 NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 and
- 20 encompasses an epitope of PCIP such that an antibody raised against the peptide forms a specific immune complex with PCIP. Preferably, the antigenic peptide comprises at least 10 amino acid residues, more preferably at least 15 amino acid residues, even more preferably at least 20 amino acid residues, and most preferably at least 30 amino acid residues.
- 25 Preferred epitopes encompassed by the antigenic peptide are regions of PCIP that are located on the surface of the protein, *e.g.*, hydrophilic regions, as well as regions with high antigenicity.

- A PCIP immunogen typically is used to prepare antibodies by immunizing a suitable subject, (*e.g.*, rabbit, goat, mouse or other mammal) with the immunogen. An
- 30 appropriate immunogenic preparation can contain, for example, recombinantly expressed PCIP protein or a chemically synthesized PCIP polypeptide. The preparation

can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar immunostimulatory agent. Immunization of a suitable subject with an immunogenic PCIP preparation induces a polyclonal anti-PCIP antibody response.

Accordingly, another aspect of the invention pertains to anti-PCIP antibodies.

- 5 The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site which specifically binds (immunoreacts with) an antigen, such as PCIP. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and F(ab')₂ fragments which can be generated by treating the
- 10 antibody with an enzyme such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind PCIP. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of PCIP. A monoclonal antibody composition
- 15 thus typically displays a single binding affinity for a particular PCIP protein with which it immunoreacts.

- Polyclonal anti-PCIP antibodies can be prepared as described above by immunizing a suitable subject with a PCIP immunogen. The anti-PCIP antibody titer in the immunized subject can be monitored over time by standard techniques, such as with
- 20 an enzyme linked immunosorbent assay (ELISA) using immobilized PCIP. If desired, the antibody molecules directed against PCIP can be isolated from the mammal (*e.g.*, from the blood) and further purified by well known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the anti-PCIP antibody titers are highest, antibody-producing cells can be
- 25 obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497) (see also, Brown *et al.* (1981) *J. Immunol.* 127:539-46; Brown *et al.* (1980) *J. Biol. Chem.* 255:4980-83; Yeh *et al.* (1976) *Proc. Natl. Acad. Sci. USA* 76:2927-31; and Yeh *et al.* (1982) *Int. J. Cancer* 29:269-75), the
- 30 more recent human B cell hybridoma technique (Kozbor *et al.* (1983) *Immunol Today* 4:72), the EBV-hybridoma technique (Cole *et al.* (1985), *Monoclonal Antibodies and*

- Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing monoclonal antibody hybridomas is well known (see generally R. H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); E. A. Lerner (1981) *Yale J. Biol. Med.*, 54:387-402; M. L. Gefter *et al.* (1977) *Somatic Cell Genet.* 3:231-36). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a PCIP immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds PCIP.
- 10 Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating an anti-PCIP monoclonal antibody (see, e.g., G. Galfre *et al.* (1977) *Nature* 266:55052; Gefter *et al.* *Somatic Cell Genet.*, cited *supra*; Lerner, *Yale J. Biol. Med.*, cited *supra*; Kenneth, *Monoclonal Antibodies*, cited *supra*). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods which also would be useful. Typically, the immortal cell line (e.g., a myeloma cell line) is derived from the same mammalian species as the lymphocytes. For example, murine hybridomas can be made by fusing lymphocytes from a mouse immunized with an immunogenic preparation of the present invention with an immortalized mouse cell line. Preferred immortal cell lines are mouse myeloma cell lines that are sensitive to culture medium containing hypoxanthine, aminopterin and thymidine ("HAT medium"). Any of a number of myeloma cell lines can be used as a fusion partner according to standard techniques, e.g., the P3-NS1/1-Ag4-1, P3-x63-Ag8.653 or Sp2/O-Ag14 myeloma lines. These myeloma lines are available from ATCC. Typically, HAT-sensitive mouse myeloma cells are fused to mouse splenocytes using polyethylene glycol ("PEG"). Hybridoma cells resulting from the fusion are then selected using HAT medium, which kills unfused and unproductively fused myeloma cells (unfused splenocytes die after several days because they are not transformed). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind PCIP, e.g., using a standard ELISA assay.

- Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-PCIP antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with PCIP to thereby isolate immunoglobulin library members that bind PCIP.
- 5 Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, Ladner *et al.* U.S.
- 10 Patent No. 5,223,409; Kang *et al.* PCT International Publication No. WO 92/18619; Dower *et al.* PCT International Publication No. WO 91/17271; Winter *et al.* PCT International Publication WO 92/20791; Markland *et al.* PCT International Publication No. WO 92/15679; Breitling *et al.* PCT International Publication WO 93/01288; McCafferty *et al.* PCT International Publication No. WO 92/01047; Garrard *et al.* PCT
- 15 International Publication No. WO 92/09690; Ladner *et al.* PCT International Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Husz *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J* 12:725-734; Hawkins *et al.* (1992) *J. Mol. Biol.* 226:889-896; Clarkson *et al.* (1991) *Nature* 352:624-628; Gram *et al.* (1992) *Proc. Natl. Acad.*
- 20 *Sci. USA* 89:3576-3580; Garrad *et al.* (1991) *Bio/Technology* 9:1373-1377; Hoogenboom *et al.* (1991) *Nuc. Acid Res.* 19:4133-4137; Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA* 88:7978-7982; and McCafferty *et al.* *Nature* (1990) 348:552-554.
- Additionally, recombinant anti-PCIP antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be
- 25 made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in Robinson *et al.* International Application No. PCT/US86/02269; Akira, *et al.* European Patent Application 184,187; Taniguchi, M., European Patent Application 171,496;
- 30 Morrison *et al.* European Patent Application 173,494; Neuberger *et al.* PCT International Publication No. WO 86/01533; Cabilly *et al.* U.S. Patent No. 4,816,567;

Cabilly *et al.* European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu *et al.* (1987) *J. Immunol.* 139:3521-3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Canc. Res.* 47:999-1005; Wood *et al.* (1985) 5 *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559; Morrison, S. L. (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *BioTechniques* 4:214; Winter U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeven *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

- An anti-PCIP antibody (*e.g.*, monoclonal antibody) can be used to isolate PCIP 10 by standard techniques, such as affinity chromatography or immunoprecipitation. An anti-PCIP antibody can facilitate the purification of natural PCIP from cells and of recombinantly produced PCIP expressed in host cells. Moreover, an anti-PCIP antibody can be used to detect PCIP protein (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the abundance and pattern of expression of the PCIP protein. Anti-PCIP 15 antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling (*i.e.*, physically linking) the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, 20 bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, 25 dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a PCIP protein (or a portion thereof). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" can be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell, which means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operatively linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for

example, in Goeddel; *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (e.g., 5 tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as 10 described herein (e.g., PCIP proteins, mutant forms of PCIP proteins, fusion proteins, and the like).

The recombinant expression vectors of the invention can be designed for expression of PCIP proteins in prokaryotic or eukaryotic cells. For example, PCIP proteins can be expressed in bacterial cells such as *E. coli*, insect cells (using 15 baculovirus expression vectors) yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

20 Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 25 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification. Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and 30 their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX (Pharmacia Biotech Inc; Smith, D.B.

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and Johnson, K.S. (1988) *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

Purified fusion proteins can be utilized in PCIP activity assays, (e.g., direct
5 assays or competitive assays described in detail below), or to generate antibodies specific for PCIP proteins, for example. In a preferred embodiment, a PCIP fusion protein expressed in a retroviral expression vector of the present invention can be utilized to infect bone marrow cells which are subsequently transplanted into irradiated recipients. The pathology of the subject recipient is then examined after sufficient time
10 has passed (e.g., six (6) weeks).

Examples of suitable inducible non-fusion *E. coli* expression vectors include pTrc (Amann *et al.*, (1988) *Gene* 69:301-315) and pET 11d (Studier *et al.*, *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 60-89). Target gene expression from the pTrc vector relies on host
15 RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter mediated by a coexpressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5
20 promoter.

One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave the recombinant protein (Gottesman, S., *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, California (1990) 119-128). Another
25 strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, (1992) *Nucleic Acids Res.* 20:2111-2118). Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

30 In another embodiment, the PCIP expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYEpSec1 (Baldari, et

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al., (1987) *Embo J.* 6:229-234), pMFA (Kurjan and Herskowitz, (1982) *Cell* 30:933-943), pJRY88 (Schultz *et al.*, (1987) *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and picZ (InVitrogen Corp, San Diego, CA).

Alternatively, PCIP proteins can be expressed in insect cells using baculovirus expression vectors. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.* (1983) *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers (1989) *Virology* 170:31-39).

In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, B. (1987) *Nature* 329:840) and pMT2PC (Kaufman *et al.* (1987) *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements. For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.* (1987) *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton (1988) *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and Baltimore (1989) *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.* (1983) *Cell* 33:729-740; Queen and Baltimore (1983) *Cell* 33:741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle (1989) *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.* (1985) *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No. 4,873,316 and European Application Publication No. 264,166). Developmentally-

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regulated promoters are also encompassed, for example the murine hox promoters (Kessel and Gruss (1990) *Science* 249:374-379) and the α -fetoprotein promoter (Campes and Tilghman (1989) *Genes Dev.* 3:537-546).

- The invention further provides a recombinant expression vector comprising a
- 5 DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operatively linked to a regulatory sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to PCIP mRNA. Regulatory sequences operatively linked to a nucleic acid cloned in the antisense orientation can be chosen which direct
- 10 the continuous expression of the antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid or attenuated virus in which antisense nucleic acids are produced under the control of a
- 15 high efficiency regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub, H. *et al.*, Antisense RNA as a molecular tool for genetic analysis, *Reviews - Trends in Genetics*, Vol. 1(1) 1986.

- Another aspect of the invention pertains to host cells into which a recombinant
- 20 expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be
- 25 identical to the parent cell, but are still included within the scope of the term as used herein.

- A host cell can be any prokaryotic or eukaryotic cell. For example, a PCIP protein can be expressed in bacterial cells such as *E. coli*, insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other
- 30 suitable host cells are known to those skilled in the art.

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- Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid (*e.g.*, DNA) into a host cell, including
- 5 calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989), and other laboratory manuals.
- 10 For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred
- 15 selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid encoding a selectable marker can be introduced into a host cell on the same vector as that encoding a PCIP protein or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid can be identified by drug selection (*e.g.*, cells that have incorporated the selectable
- 20 marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce (*i.e.*, express) a PCIP protein. Accordingly, the invention further provides methods for producing a PCIP protein using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of

25 invention (into which a recombinant expression vector encoding a PCIP protein has been introduced) in a suitable medium such that a PCIP protein is produced. In another embodiment, the method further comprises isolating a PCIP protein from the medium or the host cell.

The host cells of the invention can also be used to produce non-human transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which PCIP-coding sequences have been

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- introduced. Such host cells can then be used to create non-human transgenic animals in which exogenous PCIP sequences have been introduced into their genome or homologous recombinant animals in which endogenous PCIP sequences have been altered. Such animals are useful for studying the function and/or activity of a PCIP and
- 5 for identifying and/or evaluating modulators of PCIP activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, and the like. A transgene is exogenous DNA
- 10 which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, a "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous PCIP gene has been
- 15 altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

A transgenic animal of the invention can be created by introducing a PCIP-encoding nucleic acid into the male pronuclei of a fertilized oocyte, *e.g.*, by

20 microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. The PCIP cDNA sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 can be introduced as a transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of a human PCIP gene, such as a mouse or rat PCIP gene, can be used as a transgene. Alternatively,

25 a PCIP gene homologue, such as another PCIP family member, can be isolated based on hybridization to the PCIP cDNA sequences of SEQ ID NO:1, SEQ ID NO:3 SEQ ID

- NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71 or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994 (described further in subsection I above) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to a PCIP transgene to direct expression of a PCIP protein to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, both by Leder *et al.*, U.S. Patent No. 4,873,191 by Wagner *et al.* and in Hogan, B., *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of a PCIP transgene in its genome and/or expression of PCIP mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a PCIP protein can further be bred to other transgenic animals carrying other transgenes.

To create a homologous recombinant animal, a vector is prepared which contains at least a portion of a PCIP gene into which a deletion, addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the PCIP gene. The PCIP gene can be a human gene (*e.g.*, the cDNA of SEQ ID NO:1), but more preferably, is a non-human homologue of a human PCIP gene (*e.g.*, the cDNA of SEQ ID NO:3 or 5). For example, a mouse PCIP gene can be used to construct a homologous recombination vector suitable for altering an endogenous PCIP gene in the mouse genome. In a preferred embodiment, the vector is designed such that, upon homologous

recombination, the endogenous PCIP gene is functionally disrupted (*i.e.*, no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous PCIP gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous PCIP protein). In the homologous recombination vector, the altered portion of the PCIP gene is flanked at its 5' and 3' ends by additional nucleic acid sequence of the PCIP gene to allow for homologous recombination to occur between the exogenous PCIP gene carried by the vector and an endogenous PCIP gene in an embryonic stem cell. The additional flanking PCIP nucleic acid sequence is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see *e.g.*, Thomas, K.R. and Capecchi, M. R. (1987) *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced PCIP gene has homologously recombined with the endogenous PCIP gene are selected (see *e.g.*, Li, E. *et al.* (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see *e.g.*, Bradley, A. in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E.J. Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, A. (1991) *Current Opinion in Biotechnology* 2:823-829 and in PCT International Publication Nos.: WO 90/11354 by Le Mouellec *et al.*; WO 91/01140 by Smithies *et al.*; WO 92/0968 by Zijlstra *et al.*; and WO 93/04169 by Berns *et al.*

In another embodiment, transgenic non-humans animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For

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a description of the *cre/loxP* recombinase system, see, e.g., Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.* (1991) *Science* 251:1351-1355. If a *cre/loxP* recombinase system is used to regulate expression of the transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, e.g., by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

10 Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut, I. *et al.* (1997) *Nature* 385:810-813 and PCT International Publication Nos. WO 97/07668 and WO 97/07669. In brief, a cell, e.g., a somatic cell, from the transgenic animal can be isolated and induced to exit the growth cycle and enter G₀ phase. The quiescent cell can then be fused, e.g., through 15 the use of electrical pulses, to an enucleated oocyte from an animal of the same species from which the quiescent cell is isolated. The reconstructed oocyte is then cultured such that it develops to morula or blastocyst and then transferred to pseudopregnant female foster animal. The offspring borne of this female foster animal will be a clone of the animal from which the cell, e.g., the somatic cell, is isolated.

20

IV. Pharmaceutical Compositions

The PCIP nucleic acid molecules, fragments of PCIP proteins, and anti-PCIP antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such 25 compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and 30 agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof

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in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

- A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include
- 5 parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents;
 - 10 antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be
 - 15 enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

- Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For
- 20 intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as
 - 25 bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of
 - 30 surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol,

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ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for
5 example, aluminum monostearate and gelatin.

Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a fragment of a PCIP protein or an anti-PCIP antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared
10 by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously
15 sterile-filtered solution thereof.

Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared
20 using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as
25 microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

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For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

- Systemic administration can also be by transmucosal or transdermal means. For
- 5 transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active
- 10 compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

- 15 In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid.
- 20 Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled
- 25 in the art, for example, as described in U.S. Patent No. 4,522,811.

- It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound
- 30 calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are

dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

Toxicity and therapeutic efficacy of such compounds can be determined by

- 5 standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. While
10 compounds that exhibit toxic side effects may be used, care should be taken to design a delivery system that targets such compounds to the site of affected tissue in order to minimize potential damage to uninfected cells and, thereby, reduce side effects.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies

- 15 preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a
20 circulating plasma concentration range that includes the IC50 (*i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Such information can be used to more accurately determine useful doses in humans. Levels in plasma may be measured, for example, by high performance liquid chromatography.

- 25 As defined herein, a therapeutically effective amount of protein or polypeptide (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The skilled artisan will appreciate that certain
30 factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health

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and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of a protein, polypeptide, or antibody can include a single treatment or, preferably, can include a series of treatments.

- In a preferred example, a subject is treated with antibody, protein, or polypeptide
- 5 in the range of between about 0.1 to 20 mg/kg body weight, one time per week for
between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between
about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated
that the effective dosage of antibody, protein, or polypeptide used for treatment may
10 increase or decrease over the course of a particular treatment. Changes in dosage may
result and become apparent from the results of diagnostic assays as described herein.

The present invention encompasses agents which modulate expression
or activity. An agent may, for example, be a small molecule. For example, such small
molecules include, but are not limited to, peptides, peptidomimetics, amino acids, amino
15 acid analogs, polynucleotides, polynucleotide analogs, nucleotides, nucleotide analogs,
organic or inorganic compounds (i.e., including heteroorganic and organometallic
compounds) having a molecular weight less than about 10,000 grams per mole, organic
or inorganic compounds having a molecular weight less than about 5,000 grams per
mole, organic or inorganic compounds having a molecular weight less than about 1,000
20 grams per mole, organic or inorganic compounds having a molecular weight less than
about 500 grams per mole, and salts, esters, and other pharmaceutically acceptable forms of such
compounds.

It is understood that appropriate doses of small molecule agents depends upon a
25 number of factors within the ken of the ordinarily skilled physician, veterinarian, or
researcher. The dose(s) of the small molecule will vary, for example, depending upon
the identity, size, and condition of the subject or sample being treated, further depending
upon the route by which the composition is to be administered, if applicable, and the
effect which the practitioner desires the small molecule to have upon the nucleic acid or
30 polypeptide of the invention.

Exemplary doses include milligram or microgram amounts of the small molecule per kilogram of subject or sample weight (*e.g.*, about 1microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1microgram per kilogram to about 50 micrograms per kilogram).

- 5 It is furthermore understood that appropriate doses of a small molecule depend upon the potency of the small molecule with respect to the expression or activity to be modulated. Such appropriate doses may be determined using the assays described herein. When one or more of these small molecules is to be administered to an animal (*e.g.*, a human) in 10 order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher may, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of 15 the specific compound employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

- Further, an antibody (or fragment thereof) may be conjugated to a therapeutic 20 moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, 25 glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, 30 dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.*, daunorubicin (formerly daunomycin) and

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doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

- The conjugates of the invention can be used for modifying a given biological response, the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, alpha.-interferon, beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

- Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev., 62:119-58 (1982). Alternatively, an antibody can be conjugated to a second antibody to Form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980.

- The nucleic acid molecules of the invention can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (see U.S. Patent 5,328,470) or by

stereotactic injection (see e.g., Chen *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively, where the complete gene delivery 5 vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

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V. Uses and Methods of the Invention

The nucleic acid molecules, proteins, protein homologues, and antibodies described herein can be used in one or more of the following methods: a) screening assays; b) predictive medicine (e.g., diagnostic assays, prognostic assays, monitoring 15 clinical trials, and pharmacogenetics); and c) methods of treatment (e.g., therapeutic and prophylactic). As described herein, a PCIP protein of the invention has one or more of the following activities: (1) it interacts with (e.g., binds to) a potassium channel protein or portion thereof; (2) it regulates the phosphorylation state of a potassium channel protein or portion thereof; (3) it associates with (e.g., binds to) calcium and can, for 20 example, act as a calcium dependent kinase, e.g., phosphorylate a potassium channel or a G-protein coupled receptor in a calcium-dependent manner; (4) it associates with (e.g., binds to) calcium and can, for example, act as a calcium dependent transcription factor; (5) it modulates a potassium channel mediated activity in a cell (e.g., a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) it modulates chromatin 25 formation in a cell, e.g., a neuronal or cardiac cell; (7) it modulates vesicular traffic and protein transport in a cell, e.g., a neuronal or cardiac cell; (8) it modulates cytokine signaling in a cell, e.g., a neuronal or cardiac cell; (9) it regulates the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (10) it modulates cellular proliferation; (11) it modulates the release of neurotransmitters; (12) 30 it modulates membrane excitability; (13) it influences the resting potential of membranes; (14) it modulates wave forms and frequencies of action potentials; and (15)

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- it modulates thresholds of excitation and, thus, can be used to, for example, (1) modulate the activity of a potassium channel protein or portion thereof; (2) modulate the phosphorylation state of a potassium channel protein or portion thereof; (3) modulate the phosphorylation state of a potassium channel or a G-protein coupled receptor in a
- 5 calcium-dependent manner; (4) associate with (*e.g.*, bind to) calcium and act as a calcium dependent transcription factor; (5) modulate a potassium channel mediated activity in a cell (*e.g.*, a neuronal or cardiac cell) to, for example, beneficially affect the cell; (6) modulate chromatin formation in a cell, *e.g.*, a neuronal or cardiac cell; (7) modulate vesicular traffic and protein transport in a cell, *e.g.*, a neuronal or cardiac cell;
- 10 (8) modulate cytokine signaling in a cell, *e.g.*, a neuronal or cardiac cell; (9) regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton; (10) modulate cellular proliferation; (11) modulate the release of neurotransmitters; (12) modulate membrane excitability; (13) influence the resting potential of membranes; (14) modulate wave forms and frequencies of action potentials;
- 15 and (15) modulate thresholds of excitation.

The isolated nucleic acid molecules of the invention can be used, for example, to express PCIP protein (*e.g.*, via a recombinant expression vector in a host cell in gene therapy applications), to detect PCIP mRNA (*e.g.*, in a biological sample) or a genetic alteration in a PCIP gene, and to modulate PCIP activity, as described further below.

- 20 The PCIP proteins can be used to treat disorders characterized by insufficient or excessive production of a PCIP substrate or production of PCIP inhibitors. In addition, the PCIP proteins can be used to screen for naturally occurring PCIP substrates, to screen for drugs or compounds which modulate PCIP activity, as well as to treat disorders characterized by insufficient or excessive production of PCIP protein or
- 25 production of PCIP protein forms which have decreased or aberrant activity compared to PCIP wild type protein (*e.g.*, CNS disorders such as neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and
- 30 Jakob-Creutzfieldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or

- phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or cardiovascular disorders such as sinus node dysfunction, angina, heart failure,
- 5 hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia). Moreover, the anti-PCIP antibodies of the invention can be used to detect and isolate PCIP proteins, regulate the bioavailability of PCIP proteins, and modulate PCIP activity.

10

A. Screening Assays:

- The invention provides a method (also referred to herein as a "screening assay") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, small molecules or other drugs) which bind to PCIP proteins, have a 15 stimulatory or inhibitory effect on, for example, PCIP expression or PCIP activity, or have a stimulatory or inhibitory effect on, for example, the expression or activity of PCIP substrate.

- In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a PCIP protein or polypeptide or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to or modulate the activity of a PCIP protein or polypeptide or biologically active portion thereof. The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable 20 parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. (1997) 25 *Anticancer Drug Des.* 12:145).

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Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten (1992) *Biotechniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (Ladner USP 5,223,409), spores (Ladner USP 10 '409), plasmids (Cull *et al.* (1992) *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390); (Devlin (1990) *Science* 249:404-406); (Cwirla *et al.* (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382); (Felici (1991) *J. Mol. Biol.* 222:301-310); (Ladner *supra*.)

In one embodiment, an assay is a cell-based assay in which a cell which expresses a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate PCIP activity, *e.g.*, binding to a potassium channel or a portion thereof, is determined. Determining the ability of the test compound to modulate PCIP activity can be accomplished by monitoring, for example, the release of a neurotransmitter, *e.g.*, dopamine, from a cell which expresses PCIP such as a neuronal cell, *e.g.*, a substantia nigra neuronal cell, or a cardiac cell. Furthermore, determining the ability of the test compound to modulate PCIP activity can be accomplished by monitoring, for example, the I_{to} current or the release of a neurotransmitter from a cell which expresses PCIP such as a cardiac cell. Currents in cells, *e.g.*, the I_{to} current, can be measured using the patch-clamp technique as described in the Examples section using the techniques described in, for example, Hamill *et al.* 1981. *Pfluegers Arch.* 391: 85-100). The cell, for example, can be of mammalian origin. Determining the ability of the test compound to modulate the ability of PCIP to bind to a substrate can be accomplished, for example, by coupling the PCIP substrate with a radioisotope or enzymatic label such that binding of the PCIP substrate to PCIP can be determined by detecting the labeled PCIP substrate in a complex. For example, compounds (*e.g.*, PCIP substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or 3H , either

directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, compounds can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

- It is also within the scope of this invention to determine the ability of a compound (*e.g.*, PCIP substrate) to interact with PCIP without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a compound with PCIP without the labeling of either the compound or the PCIP.
- 10 McConnell, H. M. *et al.* (1992) *Science* 257:1906-1912. As used herein, a "microphysiometer" (*e.g.*, Cytosensor) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a compound and PCIP.
- 15 In another embodiment, an assay is a cell-based assay comprising contacting a cell expressing a PCIP target molecule (*e.g.*, a potassium channel or a fragment thereof) with a test compound and determining the ability of the test compound to modulate (*e.g.* stimulate or inhibit) the activity of the PCIP target molecule. Determining the ability of the test compound to modulate the activity of a PCIP target molecule can be
- 20 accomplished, for example, by determining the ability of the PCIP protein to bind to or interact with the PCIP target molecule, *e.g.*, a potassium channel or a fragment thereof.

Determining the ability of the PCIP protein or a biologically active fragment thereof, to bind to or interact with a PCIP target molecule can be accomplished by one of the methods described above for determining direct binding. In a preferred embodiment, 25 determining the ability of the PCIP protein to bind to or interact with a PCIP target molecule can be accomplished by determining the activity of the target molecule. For example, the activity of the target molecule can be determined by detecting induction of a cellular second messenger of the target (*i.e.*, intracellular Ca^{2+} , diacylglycerol, IP_3 , and the like), detecting catalytic/enzymatic activity of the target an appropriate substrate, 30 detecting the induction of a reporter gene (comprising a target-responsive regulatory element operatively linked to a nucleic acid encoding a detectable marker, *e.g.*,

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luciferase), or detecting a target-regulated cellular response such as the release of a neurotransmitter.

- In yet another embodiment, an assay of the present invention is a cell-free assay in which a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to bind to the PCIP protein or biologically active portion thereof is determined. Preferred biologically active portions of the PCIP proteins to be used in assays of the present invention include fragments which participate in interactions with non-PCIP molecules, *e.g.*, potassium channels or fragments thereof, or fragments with high surface probability scores. Binding of the test compound to the PCIP protein can be determined either directly or indirectly as described above. In a preferred embodiment, the assay includes contacting the PCIP protein or biologically active portion thereof with a known compound which binds PCIP to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with a PCIP protein, wherein determining the ability of the test compound to interact with a PCIP protein comprises determining the ability of the test compound to preferentially bind to PCIP or biologically active portion thereof as compared to the known compound.

- In another embodiment, the assay is a cell-free assay in which a PCIP protein or biologically active portion thereof is contacted with a test compound and the ability of the test compound to modulate (*e.g.*, stimulate or inhibit) the activity of the PCIP protein or biologically active portion thereof is determined. Determining the ability of the test compound to modulate the activity of a PCIP protein can be accomplished, for example, by determining the ability of the PCIP protein to bind to a PCIP target molecule by one of the methods described above for determining direct binding. Determining the ability of the PCIP protein to bind to a PCIP target molecule can also be accomplished using a technology such as real-time Biomolecular Interaction Analysis (BIA). Sjolander, S. and Urbaniczky, C. (1991) *Anal. Chem.* 63:2338-2345 and Szabo *et al.* (1995) *Curr. Opin. Struct. Biol.* 5:699-705. As used herein, "BIA" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the optical phenomenon of surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

In an alternative embodiment, determining the ability of the test compound to modulate the activity of a PCIP protein can be accomplished by determining the ability of the PCIP protein to further modulate the activity of a downstream effector of a PCIP target molecule. For example, the activity of the effector molecule on an appropriate target can be determined or the binding of the effector to an appropriate target can be determined as previously described.

In yet another embodiment, the cell-free assay involves contacting a PCIP protein or biologically active portion thereof with a known compound which binds the PCIP protein to form an assay mixture, contacting the assay mixture with a test compound, and determining the ability of the test compound to interact with the PCIP protein, wherein determining the ability of the test compound to interact with the PCIP protein comprises determining the ability of the PCIP protein to preferentially bind to or modulate the activity of a PCIP target molecule.

The cell-free assays of the present invention are amenable to use of both soluble and/or membrane-bound forms of isolated proteins. In the case of cell-free assays in which a membrane-bound form of an isolated protein is used (e.g., a potassium channel) it may be desirable to utilize a solubilizing agent such that the membrane-bound form of the isolated protein is maintained in solution. Examples of such solubilizing agents include non-ionic detergents such as n-octylglucoside, n-dodecylglucoside, n-dodecylmaltoside, octanoyl-N-methylglucamide, decanoyl-N-methylglucamide, Triton® X-100, Triton® X-114, Thesit®, Isotridecypoly(ethylene glycol ether)_n, 3-[(3-cholamidopropyl)dimethylammonio]-1-propane sulfonate (CHAPS), 3-[(3-cholamidopropyl)dimethylammonio]-2-hydroxy-1-propane sulfonate (CHAPSO), or N-dodecyl=N,N-dimethyl-3-ammonio-1-propane sulfonate.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either PCIP or its target molecule to facilitate separation of complexed from uncomplexed forms of one or both of the proteins, as well as to accommodate automation of the assay. Binding of a test compound to a PCIP protein, or interaction of a PCIP protein with a target molecule in the presence and absence of a candidate compound, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates,

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- test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein can be provided which adds a domain that allows one or both of the proteins to be bound to a matrix. For example, glutathione-S-transferase/ PCIP fusion proteins or glutathione-S-transferase/target fusion proteins can be adsorbed onto glutathione sepharose beads
- 5 (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtitre plates, which are then combined with the test compound or the test compound and either the non-adsorbed target protein or PCIP protein, and the mixture incubated under conditions conducive to complex formation (*e.g.*, at physiological conditions for salt and pH). Following incubation, the beads or microtitre plate wells are washed to remove any unbound
- 10 components, the matrix immobilized in the case of beads, complex determined either directly or indirectly, for example, as described above. Alternatively, the complexes can be dissociated from the matrix, and the level of PCIP binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a PCIP protein or a PCIP target molecule can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated PCIP protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies reactive with PCIP protein or target molecules but which do not interfere with binding of the PCIP protein to its target molecule can be derivatized to the wells of the plate, and unbound target or PCIP protein trapped in the wells by antibody conjugation. Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies reactive with the PCIP protein or target molecule, as well as enzyme-linked assays which rely on detecting an enzymatic activity associated with the PCIP protein or target molecule.

In a preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate vesicular traffic and protein transport in a cell, *e.g.*, a neuronal or cardiac cell, using the assays described in, for example, Komada M. *et al.* (1999) *Genes Dev.*13(11):1475-85, and Roth M.G. *et*

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al. (1999) *Chem. Phys. Lipids.* 98(1-2):141-52, the contents of which are incorporated herein by reference.

- In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to regulate the phosphorylation state of a potassium channel protein or portion thereof, using for example, an *in vitro* kinase assay. Briefly, a PCIP target molecule, e.g., an immunoprecipitated potassium channel from a cell line expressing such a molecule, can be incubated with the PCIP protein and radioactive ATP, e.g., [γ -³²P] ATP, in a buffer containing MgCl₂ and MnCl₂, e.g., 10 mM MgCl₂ and 5 mM MnCl₂. Following the 5 incubation, the immunoprecipitated PCIP target molecule, e.g., the potassium channel, can be separated by SDS-polyacrylamide gel electrophoresis under reducing conditions, transferred to a membrane, e.g., a PVDF membrane, and autoradiographed. The appearance of detectable bands on the autoradiograph indicates that the PCIP substrate, e.g., the potassium channel, has been phosphorylated. Phosphoaminoacid analysis of the 10 phosphorylated substrate can also be performed in order to determine which residues on the PCIP substrate are phosphorylated. Briefly, the radiophosphorylated protein band can be excised from the SDS gel and subjected to partial acid hydrolysis. The products can then be separated by one-dimensional electrophoresis and analyzed on, for example, a phosphoimager and compared to ninhydrin-stained phosphoaminoacid standards.
- 15 Assays such as those described in, for example, Tamaskovic R. *et al.* (1999) *Biol. Chem.* 380(5):569-78, the contents of which are incorporated herein by reference, can also be used.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to associate with 20 (e.g., bind) calcium, using for example, the assays described in Liu L. (1999) *Cell Signal.* 11(5):317-24 and Kawai T. *et al.* (1999) *Oncogene* 18(23):3471-80, the contents of which are incorporated herein by reference.

In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate 25 chromatin formation in a cell, using for example, the assays described in Okuwaki M. *et*

al. (1998) *J. Biol. Chem.* 273(51):34511-8 and Miyaji-Yamaguchi M. (1999) *J. Mol. Biol.* 290(2): 547-557, the contents of which are incorporated herein by reference.

In yet another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate 5 cellular proliferation, using for example, the assays described in Baker F.L. *et al.* (1995) *Cell Prolif.* 28(1):1-15, Cheviron N. *et al.* (1996) *Cell Prolif.* 29(8):437-46, Hu Z.W. *et al.* (1999) *J. Pharmacol. Exp. Ther.* 290(1):28-37 and Elliott K. *et al.* (1999) *Oncogene* 18(24):3564-73, the contents of which are incorporated herein by reference.

In a preferred embodiment, candidate or test compounds or agents are tested for 10 their ability to inhibit or stimulate a PCIP molecule's ability to regulate the association of a potassium channel protein or portion thereof with the cellular cytoskeleton, using for example, the assays described in Gonzalez C. *et al.* (1998) *Cell Mol. Biol.* 44(7):1117-27 and Chia C.P. *et al.* (1998) *Exp. Cell Res.* 244(1):340-8, the contents of which are incorporated herein by reference.

15 In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate membrane excitability, using for example, the assays described in Bar-Sagi D. *et al.* (1985) *J. Biol. Chem.* 260(8):4740-4 and Barker J.L. *et al.* (1984) *Neurosci. Lett.* 47(3):313-8, the contents of which are incorporated herein by reference.

20 In another preferred embodiment, candidate or test compounds or agents are tested for their ability to inhibit or stimulate a PCIP molecule's ability to modulate cytokine signaling in a cell, e.g., a neuronal or cardiac cell, the assays described in Nakashima Y. *et al.* (1999) *J. Bone Joint Surg. Am.* 81(5):603-15, the contents of which are incorporated herein by reference.

25 In another embodiment, modulators of PCIP expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of PCIP mRNA or protein in the cell is determined. The level of expression of PCIP mRNA or protein in the presence of the candidate compound is compared to the level of expression of PCIP mRNA or protein in the absence of the candidate compound. The 30 candidate compound can then be identified as a modulator of PCIP expression based on this comparison. For example, when expression of PCIP mRNA or protein is greater

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(statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of PCIP mRNA or protein expression. Alternatively, when expression of PCIP mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of PCIP mRNA or protein expression. The level of PCIP mRNA or protein expression in the cells can be determined by methods described herein for detecting PCIP mRNA or protein.

- In yet another aspect of the invention, the PCIP proteins can be used as "bait proteins" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Patent No. 10 5,283,317; Zervos *et al.* (1993) *Cell* 72:223-232; Madura *et al.* (1993) *J. Biol. Chem.* 268:12046-12054; Bartel *et al.* (1993) *Biotechniques* 14:920-924; Iwabuchi *et al.* (1993) *Oncogene* 8:1693-1696; and Brent WO94/10300), to identify other proteins, which bind to or interact with PCIP ("PCIP-binding proteins" or "PCIP-bp") and are involved in PCIP activity (described in more detail in the Examples section below).
15 Such PCIP-binding proteins are also likely to be involved in the propagation of signals by the PCIP proteins or PCIP targets as, for example, downstream elements of a PCIP-mediated signaling pathway. Alternatively, such PCIP-binding proteins are likely to be PCIP inhibitors.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that codes for a PCIP protein is fused to a gene encoding the DNA binding domain of a known transcription factor (e.g., GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a PCIP-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected and cell colonies

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containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the PCIP protein.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a PCIP modulating agent, an antisense PCIP nucleic acid molecule, a PCIP-specific antibody, or a PCIP-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments, *e.g.*, treatments of a CNS disorder or a cardiovascular disorder, as described herein.

15 **B. Detection Assays**

Portions or fragments of the cDNA sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. These applications are described in the subsections below.

1. Chromosome Mapping

Once the sequence (or a portion of the sequence) of a gene has been isolated, this sequence can be used to map the location of the gene on a chromosome. This process is called chromosome mapping. Accordingly, portions or fragments of the PCIP nucleotide sequences, described herein, can be used to map the location of the PCIP genes on a chromosome. The mapping of the PCIP sequences to chromosomes is an important first step in correlating these sequences with genes associated with disease.

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Briefly, PCIP genes can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp in length) from the PCIP nucleotide sequences. Computer analysis of the PCIP sequences can be used to predict primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers 5 can then be used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the PCIP sequences will yield an amplified fragment.

Somatic cell hybrids are prepared by fusing somatic cells from different mammals (e.g., human and mouse cells). As hybrids of human and mouse cells grow and divide, they gradually lose human chromosomes in random order, but retain the mouse chromosomes. By using media in which mouse cells cannot grow, because they lack a particular enzyme, but human cells can, the one human chromosome that contains the gene encoding the needed enzyme, will be retained. By using various media, panels of hybrid cell lines can be established. Each cell line in a panel contains either a single human chromosome or a small number of human chromosomes, and a full set of mouse chromosomes, allowing easy mapping of individual genes to specific human chromosomes. (D'Eustachio P. *et al.* (1983) *Science* 220:919-924). Somatic cell hybrids containing only fragments of human chromosomes can also be produced by using human chromosomes with translocations and deletions.

20 PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular sequence to a particular chromosome. Three or more sequences can be assigned per day using a single thermal cycler. Using the PCIP nucleotide sequences to design oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes. Other mapping strategies which can similarly be
25 used to map a PCIP sequence to its chromosome include *in situ* hybridization (described in Fan, Y. et al. (1990) *Proc. Natl. Acad. Sci. USA*, 87:6223-27), pre-screening with labeled flow-sorted chromosomes, and pre-selection by hybridization to chromosome specific cDNA libraries.

Fluorescence *in situ* hybridization (FISH) of a DNA sequence to a metaphase 30 chromosomal spread can further be used to provide a precise chromosomal location in one step. Chromosome spreads can be made using cells whose division has been

blocked in metaphase by a chemical such as colcemid that disrupts the mitotic spindle. The chromosomes can be treated briefly with trypsin, and then stained with Giemsa. A pattern of light and dark bands develops on each chromosome, so that the chromosomes can be identified individually. The FISH technique can be used with a DNA sequence 5 as short as 500 or 600 bases. However, clones larger than 1,000 bases have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. Preferably 1,000 bases, and more preferably 2,000 bases will suffice to get good results at a reasonable amount of time. For a review of this technique, see Verma *et al.*, Human Chromosomes: A Manual of Basic Techniques 10 (Pergamon Press, New York 1988).

Reagents for chromosome mapping can be used individually to mark a single chromosome or a single site on that chromosome, or panels of reagents can be used for marking multiple sites and/or multiple chromosomes. Reagents corresponding to noncoding regions of the genes actually are preferred for mapping purposes. Coding 15 sequences are more likely to be conserved within gene families, thus increasing the chance of cross hybridizations during chromosomal mapping.

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. (Such data are found, for example, in V. McKusick, Mendelian Inheritance in 20 Man, available on-line through Johns Hopkins University Welch Medical Library). The relationship between a gene and a disease, mapped to the same chromosomal region, can then be identified through linkage analysis (co-inheritance of physically adjacent genes), described in, for example, Egeland, J. *et al.* (1987) *Nature*, 325:783-787.

Moreover, differences in the DNA sequences between individuals affected and 25 unaffected with a disease associated with the PCIP gene, can be determined. If a mutation is observed in some or all of the affected individuals but not in any unaffected individuals, then the mutation is likely to be the causative agent of the particular disease. Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are 30 visible from chromosome spreads or detectable using PCR based on that DNA sequence.

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Ultimately, complete sequencing of genes from several individuals can be performed to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

2. Tissue Typing

- 5 The PCIP sequences of the present invention can also be used to identify individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield
10 unique bands for identification. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The sequences of the present invention are useful as additional DNA markers for RFLP (described in U.S. Patent 5,272,057).

Furthermore, the sequences of the present invention can be used to provide an alternative technique which determines the actual base-by-base DNA sequence of selected portions of an individual's genome. Thus, the PCIP nucleotide sequences described herein can be used to prepare two PCR primers from the 5' and 3' ends of the sequences. These primers can then be used to amplify an individual's DNA and subsequently sequence it.

- Panels of corresponding DNA sequences from individuals, prepared in this manner, can provide unique individual identifications, as each individual will have a unique set of such DNA sequences due to allelic differences. The sequences of the present invention can be used to obtain such identification sequences from individuals and from tissue. The PCIP nucleotide sequences of the invention uniquely represent portions of the human genome. Allelic variation occurs to some degree in the coding regions of these sequences, and to a greater degree in the noncoding regions. It is estimated that allelic variation between individual humans occurs with a frequency of about once per each 500 bases. Each of the sequences described herein can, to some degree, be used as a standard against which DNA from an individual can be compared for identification purposes. Because greater numbers of polymorphisms occur in the noncoding regions, fewer sequences are necessary to differentiate individuals. Non-

coding sequences can comfortably provide positive individual identification with a panel of perhaps 10 to 1,000 primers which each yield a noncoding amplified sequence of 100 bases. If predicted coding sequences are used, a more appropriate number of primers for positive individual identification would be 500-2,000.

- 5 If a panel of reagents from PCIP nucleotide sequences described herein is used to generate a unique identification database for an individual, those same reagents can later be used to identify tissue from that individual. Using the unique identification database, positive identification of the individual, living or dead, can be made from extremely small tissue samples.

10

3. Use of Partial PCIP Sequences in Forensic Biology

DNA-based identification techniques can also be used in forensic biology.

- Forensic biology is a scientific field employing genetic typing of biological evidence found at a crime scene as a means for positively identifying, for example, a perpetrator
15 of a crime. To make such an identification, PCR technology can be used to amplify DNA sequences taken from very small biological samples such as tissues, *e.g.*, hair or skin, or body fluids, *e.g.*, blood, saliva, or semen found at a crime scene. The amplified sequence can then be compared to a standard, thereby allowing identification of the origin of the biological sample.

20

- The sequences of the present invention can be used to provide polynucleotide reagents, *e.g.*, PCR primers, targeted to specific loci in the human genome, which can enhance the reliability of DNA-based forensic identifications by, for example, providing another "identification marker" (*i.e.* another DNA sequence that is unique to a particular individual). As mentioned above, actual base sequence information can be used for
25 identification as an accurate alternative to patterns formed by restriction enzyme generated fragments. Sequences targeted to noncoding regions are particularly appropriate for this use as greater numbers of polymorphisms occur in the noncoding regions, making it easier to differentiate individuals using this technique. Examples of polynucleotide reagents include the PCIP nucleotide sequences or portions thereof,
30 having a length of at least 20 bases, preferably at least 30 bases.

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The PCIP nucleotide sequences described herein can further be used to provide polynucleotide reagents, *e.g.*, labeled or labelable probes which can be used in, for example, an *in situ* hybridization technique, to identify a specific tissue, *e.g.*, brain tissue. This can be very useful in cases where a forensic pathologist is presented with a 5 tissue of unknown origin. Panels of such PCIP probes can be used to identify tissue by species and/or by organ type.

In a similar fashion, these reagents, *e.g.*, PCIP primers or probes can be used to screen tissue culture for contamination (*i.e.* screen for the presence of a mixture of different types of cells in a culture).

10

C. Predictive Medicine:

The present invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. 15 Accordingly, one aspect of the present invention relates to diagnostic assays for determining PCIP protein and/or nucleic acid expression as well as PCIP activity, in the context of a biological sample (*e.g.*, blood, serum, cells, tissue) to thereby determine whether an individual is afflicted with a disease or disorder, or is at risk of developing a disorder, associated with aberrant PCIP expression or activity. The invention also 20 provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with PCIP protein, nucleic acid expression or activity. For example, mutations in a PCIP gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with 25 PCIP protein, nucleic acid expression or activity.

Another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs, compounds) on the expression or activity of PCIP in clinical trials.

These and other agents are described in further detail in the following sections.

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1. Diagnostic Assays

An exemplary method for detecting the presence or absence of PCIP protein or nucleic acid in a biological sample involves obtaining a biological sample from a test subject and contacting the biological sample with a compound or an agent capable of

5 detecting PCIP protein or nucleic acid (*e.g.*, mRNA, genomic DNA) that encodes PCIP protein such that the presence of PCIP protein or nucleic acid is detected in the biological sample. A preferred agent for detecting PCIP mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to PCIP mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length PCIP nucleic acid, such as the

10 nucleic acid of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:50, SEQ ID

15 NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, or 98994, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and

20 sufficient to specifically hybridize under stringent conditions to PCIP mRNA or genomic DNA. Other suitable probes for use in the diagnostic assays of the invention are described herein.

A preferred agent for detecting PCIP protein is an antibody capable of binding to PCIP protein, preferably an antibody with a detectable label. Antibodies can be

25 polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or F(ab')₂) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is

30 directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with

biotin such that it can be detected with fluorescently labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. That is, the detection method of the invention can be used to detect PCIP mRNA, protein, or

5 genomic DNA in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of PCIP mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of PCIP protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of PCIP genomic DNA include

10 Southern hybridizations. Furthermore, *in vivo* techniques for detection of PCIP protein include introducing into a subject a labeled anti-PCIP antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

In one embodiment, the biological sample contains protein molecules from the

15 test subject. Alternatively, the biological sample can contain mRNA molecules from the test subject or genomic DNA molecules from the test subject. A preferred biological sample is a serum sample or cerebrospinal fluid isolated by conventional means from a subject.

In another embodiment, the methods further involve obtaining a control

20 biological sample from a control subject, contacting the control sample with a compound or agent capable of detecting PCIP protein, mRNA, or genomic DNA, such that the presence of PCIP protein, mRNA or genomic DNA is detected in the biological sample, and comparing the presence of PCIP protein, mRNA or genomic DNA in the control sample with the presence of PCIP protein, mRNA or genomic DNA in the test

25 sample.

The invention also encompasses kits for detecting the presence of PCIP in a biological sample. For example, the kit can comprise a labeled compound or agent capable of detecting PCIP protein or mRNA in a biological sample; means for determining the amount of PCIP in the sample; and means for comparing the amount of

30 PCIP in the sample with a standard. The compound or agent can be packaged in a

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suitable container. The kit can further comprise instructions for using the kit to detect PCIP protein or nucleic acid.

2. Prognostic Assays

- 5 The diagnostic methods described herein can furthermore be utilized to identify subjects having or at risk of developing a disease or disorder associated with aberrant PCIP expression or activity. For example, the assays described herein, such as the preceding diagnostic assays or the following assays, can be utilized to identify a subject having or at risk of developing a disorder associated with a misregulation in PCIP
- 10 protein activity or nucleic acid expression, such as a neurodegenerative disorder, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfieldt disease; a psychiatric disorder, *e.g.*, depression, schizophrenic
- 15 disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; a learning or memory disorder, *e.g.*, amnesia or age-related memory loss; a neurological disorder, *e.g.*, migraine; a pain disorder, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or a cardiovascular disorder, *e.g.*, sinus node dysfunction, angina, heart failure,
- 20 hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia.

Alternatively, the prognostic assays can be utilized to identify a subject having or at risk for developing a disorder associated with a misregulation in PCIP protein activity or nucleic acid expression, such as a potassium channel associated disorder. Thus, the present invention provides a method for identifying a disease or disorder associated with aberrant PCIP expression or activity in which a test sample is obtained from a subject and PCIP protein or nucleic acid (*e.g.*, mRNA or genomic DNA) is detected, wherein the presence of PCIP protein or nucleic acid is diagnostic for a subject having or at risk 25 of developing a disease or disorder associated with aberrant PCIP expression or activity. As used herein, a "test sample" refers to a biological sample obtained from a subject of

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interest. For example, a test sample can be a biological fluid (*e.g.*, serum), cell sample, or tissue.

- Furthermore, the prognostic assays described herein can be used to determine whether a subject can be administered an agent (*e.g.*, an agonist, antagonist,
- 5 peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) to treat a disease or disorder associated with aberrant PCIP expression or activity. For example, such methods can be used to determine whether a subject can be effectively treated with an agent for a CNS disorder or a cardiovascular disorder. Thus, the present invention provides methods for determining whether a subject can be effectively treated
- 10 with an agent for a disorder associated with aberrant PCIP expression or activity in which a test sample is obtained and PCIP protein or nucleic acid expression or activity is detected (*e.g.*, wherein the abundance of PCIP protein or nucleic acid expression or activity is diagnostic for a subject that can be administered the agent to treat a disorder associated with aberrant PCIP expression or activity).
- 15 The methods of the invention can also be used to detect genetic alterations in a PCIP gene, thereby determining if a subject with the altered gene is at risk for a disorder characterized by misregulation in PCIP protein activity or nucleic acid expression, such as a CNS disorder or a cardiovascular disorder. In preferred embodiments, the methods include detecting, in a sample of cells from the subject, the presence or absence of a
- 20 genetic alteration characterized by at least one of an alteration affecting the integrity of a gene encoding a PCIP-protein, or the mis-expression of the PCIP gene. For example, such genetic alterations can be detected by ascertaining the existence of at least one of 1) a deletion of one or more nucleotides from a PCIP gene; 2) an addition of one or more nucleotides to a PCIP gene; 3) a substitution of one or more nucleotides of a PCIP gene,
- 25 4) a chromosomal rearrangement of a PCIP gene; 5) an alteration in the level of a messenger RNA transcript of a PCIP gene, 6) aberrant modification of a PCIP gene, such as of the methylation pattern of the genomic DNA, 7) the presence of a non-wild type splicing pattern of a messenger RNA transcript of a PCIP gene, 8) a non-wild type level of a PCIP-protein, 9) allelic loss of a PCIP gene, and 10) inappropriate post-
- 30 translational modification of a PCIP-protein. As described herein, there are a large number of assays known in the art which can be used for detecting alterations in a PCIP

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gene. A preferred biological sample is a tissue or serum sample isolated by conventional means from a subject.

In certain embodiments, detection of the alteration involves the use of a probe/primer in a polymerase chain reaction (PCR) (see, e.g., U.S. Patent Nos.

- 5 4,683,195 and 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligation chain reaction (LCR) (see, e.g., Landegran *et al.* (1988) *Science* 241:1077-1080; and Nakazawa *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:360-364), the latter of which can be particularly useful for detecting point mutations in the PCIP-gene (see Abravaya *et al.* (1995) *Nucleic Acids Res.* 23:675-682). This method can include the steps of
- 10 collecting a sample of cells from a subject, isolating nucleic acid (e.g., genomic, mRNA or both) from the cells of the sample, contacting the nucleic acid sample with one or more primers which specifically hybridize to a PCIP gene under conditions such that hybridization and amplification of the PCIP-gene (if present) occurs, and detecting the presence or absence of an amplification product, or detecting the size of the
- 15 amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

- Alternative amplification methods include: self sustained sequence replication (Guatelli, J.C. *et al.*, (1990) *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh, D.Y. *et al.*, (1989) *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi, P.M. *et al.* (1988) *Bio-Technology* 6:1197), or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such
- 25 molecules are present in very low numbers.

- In an alternative embodiment, mutations in a PCIP gene from a sample cell can be identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis and compared. Differences in fragment length sizes between sample and control DNA indicates mutations in the sample DNA. Moreover, the use of sequence

specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

In other embodiments, genetic mutations in PCIP can be identified by

- 5 hybridizing a sample and control nucleic acids, e.g., DNA or RNA, to high density arrays containing hundreds or thousands of oligonucleotides probes (Cronin, M.T. *et al.* (1996) *Human Mutation* 7: 244-255; Kozal, M.J. *et al.* (1996) *Nature Medicine* 2: 753-759). For example, genetic mutations in PCIP can be identified in two dimensional arrays containing light-generated DNA probes as described in Cronin, M.T. *et al. supra.*
- 10 Briefly, a first hybridization array of probes can be used to scan through long stretches of DNA in a sample and control to identify base changes between the sequences by making linear arrays of sequential overlapping probes. This step allows the identification of point mutations. This step is followed by a second hybridization array that allows the characterization of specific mutations by using smaller, specialized probe
- 15 arrays complementary to all variants or mutations detected. Each mutation array is composed of parallel probe sets, one complementary to the wild-type gene and the other complementary to the mutant gene.

In yet another embodiment, any of a variety of sequencing reactions known in the art can be used to directly sequence the PCIP gene and detect mutations by

- 20 comparing the sequence of the sample PCIP with the corresponding wild-type (control) sequence. Examples of sequencing reactions include those based on techniques developed by Maxam and Gilbert ((1977) *Proc. Natl. Acad. Sci. USA* 74:560) or Sanger ((1977) *Proc. Natl. Acad. Sci. USA* 74:5463). It is also contemplated that any of a variety of automated sequencing procedures can be utilized when performing the
- 25 diagnostic assays ((1995) *Biotechniques* 19:448), including sequencing by mass spectrometry (see, e.g., PCT International Publication No. WO 94/16101; Cohen *et al.* (1996) *Adv. Chromatogr.* 36:127-162; and Griffin *et al.* (1993) *Appl. Biochem. Biotechnol.* 38:147-159).

Other methods for detecting mutations in the PCIP gene include methods in

- 30 which protection from cleavage agents is used to detect mismatched bases in RNA/RNA or RNA/DNA heteroduplexes (Myers *et al.* (1985) *Science* 230:1242). In general, the

- art technique of "mismatch cleavage" starts by providing heteroduplexes of formed by hybridizing (labeled) RNA or DNA containing the wild-type PCIP sequence with potentially mutant RNA or DNA obtained from a tissue sample. The double-stranded duplexes are treated with an agent which cleaves single-stranded regions of the duplex
- 5 such as which will exist due to basepair mismatches between the control and sample strands. For instance, RNA/DNA duplexes can be treated with RNase and DNA/DNA hybrids treated with S1 nuclease to enzymatically digesting the mismatched regions. In other embodiments, either DNA/DNA or RNA/DNA duplexes can be treated with hydroxylamine or osmium tetroxide and with piperidine in order to digest mismatched
- 10 regions. After digestion of the mismatched regions, the resulting material is then separated by size on denaturing polyacrylamide gels to determine the site of mutation. See, for example, Cotton *et al.* (1988) *Proc. Natl Acad Sci USA* 85:4397; Saleeba *et al.* (1992) *Methods Enzymol.* 217:286-295. In a preferred embodiment, the control DNA or RNA can be labeled for detection.
- 15 In still another embodiment, the mismatch cleavage reaction employs one or more proteins that recognize mismatched base pairs in double-stranded DNA (so called "DNA mismatch repair" enzymes) in defined systems for detecting and mapping point mutations in PCIP cDNAs obtained from samples of cells. For example, the mutY enzyme of *E. coli* cleaves A at G/A mismatches and the thymidine DNA glycosylase
- 20 from HeLa cells cleaves T at G/T mismatches (Hsu *et al.* (1994) *Carcinogenesis* 15:1657-1662). According to an exemplary embodiment, a probe based on a PCIP sequence, *e.g.*, a wild-type PCIP sequence, is hybridized to a cDNA or other DNA product from a test cell(s). The duplex is treated with a DNA mismatch repair enzyme, and the cleavage products, if any, can be detected from electrophoresis protocols or the
- 25 like. See, for example, U.S. Patent No. 5,459,039.

In other embodiments, alterations in electrophoretic mobility will be used to identify mutations in PCIP genes. For example, single strand conformation polymorphism (SSCP) may be used to detect differences in electrophoretic mobility between mutant and wild type nucleic acids (Orita *et al.* (1989) *Proc Natl. Acad. Sci USA*: 86:2766, see also Cotton (1993) *Mutat. Res.* 285:125-144; and Hayashi (1992) *Genet. Anal. Tech. Appl.* 9:73-79). Single-stranded DNA fragments of sample and

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control PCIP nucleic acids will be denatured and allowed to renature. The secondary structure of single-stranded nucleic acids varies according to sequence, the resulting alteration in electrophoretic mobility enables the detection of even a single base change.

The DNA fragments may be labeled or detected with labeled probes. The sensitivity of

- 5 the assay may be enhanced by using RNA (rather than DNA), in which the secondary structure is more sensitive to a change in sequence. In a preferred embodiment, the subject method utilizes heteroduplex analysis to separate double stranded heteroduplex molecules on the basis of changes in electrophoretic mobility (*Keen et al. (1991) Trends Genet 7:5*).

- 10 In yet another embodiment the movement of mutant or wild-type fragments in polyacrylamide gels containing a gradient of denaturant is assayed using denaturing gradient gel electrophoresis (DGGE) (*Myers et al. (1985) Nature 313:495*). When DGGE is used as the method of analysis, DNA will be modified to insure that it does not completely denature, for example by adding a GC clamp of approximately 40 bp of
15 high-melting GC-rich DNA by PCR. In a further embodiment, a temperature gradient is used in place of a denaturing gradient to identify differences in the mobility of control and sample DNA (*Rosenbaum and Reissner (1987) Biophys Chem 265:12753*).

- Examples of other techniques for detecting point mutations include, but are not limited to, selective oligonucleotide hybridization, selective amplification, or selective
20 primer extension. For example, oligonucleotide primers may be prepared in which the known mutation is placed centrally and then hybridized to target DNA under conditions which permit hybridization only if a perfect match is found (*Saiki et al. (1986) Nature 324:163; Saiki et al. (1989) Proc. Natl Acad. Sci USA 86:6230*). Such allele specific oligonucleotides are hybridized to PCR amplified target DNA or a number of different
25 mutations when the oligonucleotides are attached to the hybridizing membrane and hybridized with labeled target DNA.

Alternatively, allele specific amplification technology which depends on selective PCR amplification may be used in conjunction with the instant invention.

- Oligonucleotides used as primers for specific amplification may carry the mutation of
30 interest in the center of the molecule (so that amplification depends on differential hybridization) (*Gibbs et al. (1989) Nucleic Acids Res. 17:2437-2448*) or at the extreme 3'

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- end of one primer where, under appropriate conditions, mismatch can prevent, or reduce polymerase extension (Prossner (1993) *Tibtech* 11:238). In addition it may be desirable to introduce a novel restriction site in the region of the mutation to create cleavage-based detection (Gasparini *et al.* (1992) *Mol. Cell Probes* 6:1). It is anticipated that in certain 5 embodiments amplification may also be performed using Taq ligase for amplification (Barany (1991) *Proc. Natl. Acad. Sci USA* 88:189). In such cases, ligation will occur only if there is a perfect match at the 3' end of the 5' sequence making it possible to detect the presence of a known mutation at a specific site by looking for the presence or absence of amplification.
- 10 The methods described herein may be performed, for example, by utilizing pre-packaged diagnostic kits comprising at least one probe nucleic acid or antibody reagent described herein, which may be conveniently used, *e.g.*, in clinical settings to diagnose patients exhibiting symptoms or family history of a disease or illness involving a PCIP gene.
- 15 Furthermore, any cell type or tissue in which PCIP is expressed may be utilized in the prognostic assays described herein.

3. Monitoring of Effects During Clinical Trials

- Monitoring the influence of agents (*e.g.*, drugs) on the expression or activity of a 20 PCIP protein (*e.g.*, the modulation of membrane excitability or resting potential) can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent determined by a screening assay as described herein to increase PCIP gene expression, protein levels, or upregulate PCIP activity, can be monitored in clinical trials of subjects exhibiting decreased PCIP gene expression, protein levels, or 25 downregulated PCIP activity. Alternatively, the effectiveness of an agent determined by a screening assay to decrease PCIP gene expression, protein levels, or downregulate PCIP activity, can be monitored in clinical trials of subjects exhibiting increased PCIP gene expression, protein levels, or upregulated PCIP activity. In such clinical trials, the expression or activity of a PCIP gene, and preferably, other genes that have been 30 implicated in, for example, a potassium channel associated disorder can be used as a "read out" or markers of the phenotype of a particular cell.

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- For example, and not by way of limitation, genes, including PCIP, that are modulated in cells by treatment with an agent (*e.g.*, compound, drug or small molecule) which modulates PCIP activity (*e.g.*, identified in a screening assay as described herein) can be identified. Thus, to study the effect of agents on potassium channel associated disorders, for example, in a clinical trial, cells can be isolated and RNA prepared and analyzed for the levels of expression of PCIP and other genes implicated in the potassium channel associated disorder, respectively. The levels of gene expression (*e.g.*, a gene expression pattern) can be quantified by northern blot analysis or RT-PCR, as described herein, or alternatively by measuring the amount of protein produced, by one of the methods as described herein, or by measuring the levels of activity of PCIP or other genes. In this way, the gene expression pattern can serve as a marker, indicative of the physiological response of the cells to the agent. Accordingly, this response state may be determined before, and at various points during treatment of the individual with the agent.
- In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate identified by the screening assays described herein) including the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of a PCIP protein, mRNA, or genomic DNA in the preadministration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression or activity of the PCIP protein, mRNA, or genomic DNA in the post-administration samples; (v) comparing the level of expression or activity of the PCIP protein, mRNA, or genomic DNA in the pre-administration sample with the PCIP protein, mRNA, or genomic DNA in the post administration sample or samples; and (vi) altering the administration of the agent to the subject accordingly. For example, increased administration of the agent may be desirable to increase the expression or activity of PCIP to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent may be desirable to decrease expression or activity of PCIP to lower levels than detected, *i.e.* to decrease the effectiveness of the agent. According to such an

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embodiment, PCIP expression or activity may be used as an indicator of the effectiveness of an agent, even in the absence of an observable phenotypic response.

D. Methods of Treatment:

- 5 The present invention provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disorder or having a disorder associated with aberrant PCIP expression or activity. With regards to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored or modified, based on knowledge obtained from the field of pharmacogenomics.
- 10 "Pharmacogenomics", as used herein, refers to the application of genomics technologies such as gene sequencing, statistical genetics, and gene expression analysis to drugs in clinical development and on the market. More specifically, the term refers the study of how a patient's genes determine his or her response to a drug (*e.g.*, a patient's "drug response phenotype", or "drug response genotype".) Thus, another aspect of the
- 15 invention provides methods for tailoring an individual's prophylactic or therapeutic treatment with either the PCIP molecules of the present invention or PCIP modulators according to that individual's drug response genotype. Pharmacogenomics allows a clinician or physician to target prophylactic or therapeutic treatments to patients who will most benefit from the treatment and to avoid treatment of patients who will
- 20 experience toxic drug-related side effects.

1. Prophylactic Methods

- In one aspect, the invention provides a method for preventing in a subject, a disease or condition associated with an aberrant PCIP expression or activity, by
- 25 administering to the subject a PCIP or an agent which modulates PCIP expression or at least one PCIP activity. Subjects at risk for a disease which is caused or contributed to by aberrant PCIP expression or activity can be identified by, for example, any or a combination of diagnostic or prognostic assays as described herein. Administration of a prophylactic agent can occur prior to the manifestation of symptoms characteristic of the
- 30 PCIP aberrancy, such that a disease or disorder is prevented or, alternatively, delayed in its progression. Depending on the type of PCIP aberrancy, for example, a PCIP, PCIP

agonist or PCIP antagonist agent can be used for treating the subject. The appropriate agent can be determined based on screening assays described herein.

2. Therapeutic Methods

- 5 Another aspect of the invention pertains to methods of modulating PCIP expression or activity for therapeutic purposes. Accordingly, in an exemplary embodiment, the modulatory method of the invention involves contacting a cell with a PCIP or agent that modulates one or more of the activities of PCIP protein activity associated with the cell. An agent that modulates PCIP protein activity can be an agent
10 as described herein, such as a nucleic acid or a protein, a naturally-occurring target molecule of a PCIP protein (*e.g.*, a PCIP substrate), a PCIP antibody, a PCIP agonist or antagonist, a peptidomimetic of a PCIP agonist or antagonist, or other small molecule. In one embodiment, the agent stimulates one or more PCIP activities. Examples of such stimulatory agents include active PCIP protein and a nucleic acid molecule encoding
15 PCIP that has been introduced into the cell. In another embodiment, the agent inhibits one or more PCIP activities. Examples of such inhibitory agents include antisense PCIP nucleic acid molecules, anti-PCIP antibodies, and PCIP inhibitors. These modulatory methods can be performed *in vitro* (*e.g.*, by culturing the cell with the agent) or, alternatively, *in vivo* (*e.g.*, by administering the agent to a subject). As such, the present
20 invention provides methods of treating an individual afflicted with a disease or disorder characterized by aberrant expression or activity of a PCIP protein or nucleic acid molecule. Examples of such disorders include CNS disorders such as neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, and Jakob-Creutzfieldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety disorders, bipolar affective disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain
25 associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or cardiovascular disorders, *e.g.*, arteriosclerosis, ischemia reperfusion injury, restenosis,
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- arterial inflammation, vascular wall remodeling, ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina,
- 5 heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery disease, coronary artery spasm, or arrhythmia. In one embodiment, the method involves administering an agent (*e.g.*, an agent identified by a screening assay described herein), or combination of agents that modulates (*e.g.*, upregulates or downregulates) PCIP expression or activity.
- 10 In another embodiment, the method involves administering a PCIP protein or nucleic acid molecule as therapy to compensate for reduced or aberrant PCIP expression or activity.

A preferred embodiment of the present invention involves a method for treatment of a PCIP associated disease or disorder which includes the step of administering a 15 therapeutically effective amount of a PCIP antibody to a subject. As defined herein, a therapeutically effective amount of antibody (*i.e.*, an effective dosage) ranges from about 0.001 to 30 mg/kg body weight, preferably about 0.01 to 25 mg/kg body weight, more preferably about 0.1 to 20 mg/kg body weight, and even more preferably about 1 to 10 mg/kg, 2 to 9 mg/kg, 3 to 8 mg/kg, 4 to 7 mg/kg, or 5 to 6 mg/kg body weight. The 20 skilled artisan will appreciate that certain factors may influence the dosage required to effectively treat a subject, including but not limited to the severity of the disease or disorder, previous treatments, the general health and/or age of the subject, and other diseases present. Moreover, treatment of a subject with a therapeutically effective amount of an antibody can include a single treatment or, preferably, can include a series 25 of treatments. In a preferred example, a subject is treated with antibody in the range of between about 0.1 to 20 mg/kg body weight, one time per week for between about 1 to 10 weeks, preferably between 2 to 8 weeks, more preferably between about 3 to 7 weeks, and even more preferably for about 4, 5, or 6 weeks. It will also be appreciated that the effective dosage of antibody used for treatment may increase or decrease over 30 the course of a particular treatment. Changes in dosage may result from the results of diagnostic assays as described herein.

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Stimulation of PCIP activity is desirable in situations in which PCIP is abnormally downregulated and/or in which increased PCIP activity is likely to have a beneficial effect. For example, stimulation of PCIP activity is desirable in situations in which a PCIP is downregulated and/or in which increased PCIP activity is likely to have 5 a beneficial effect. Likewise, inhibition of PCIP activity is desirable in situations in which PCIP is abnormally upregulated and/or in which decreased PCIP activity is likely to have a beneficial effect.

3. Pharmacogenomics

- 10 The PCIP molecules of the present invention, as well as agents, or modulators which have a stimulatory or inhibitory effect on PCIP activity (*e.g.*, PCIP gene expression) as identified by a screening assay described herein can be administered to individuals to treat (prophylactically or therapeutically) potassium channel associated disorders associated with aberrant PCIP activity (*e.g.*, CNS disorders such as 15 neurodegenerative disorders, *e.g.*, Alzheimer's disease, dementias related to Alzheimer's disease (such as Pick's disease), Parkinson's and other Lewy diffuse body diseases, multiple sclerosis, amyotrophic lateral sclerosis, progressive supranuclear palsy, epilepsy, spinocerebellar ataxia, and Jakob-Creutzfeldt disease; psychiatric disorders, *e.g.*, depression, schizophrenic disorders, Korsakoff's psychosis, mania, anxiety 20 disorders, bipolar affective disorders, or phobic disorders; learning or memory disorders, *e.g.*, amnesia or age-related memory loss; neurological disorders, *e.g.*, migraine; pain disorders, *e.g.*, hyperalgesia or pain associated with musculoskeletal disorders; spinal cord injury; stroke; and head trauma; or cardiovascular disorders such as arteriosclerosis, ischemia reperfusion injury, restenosis, arterial inflammation, vascular wall remodeling, 25 ventricular remodeling, rapid ventricular pacing, coronary microembolism, tachycardia, bradycardia, pressure overload, aortic bending, coronary artery ligation, vascular heart disease, atrial fibrillation, long-QT syndrome, congestive heart failure, sinus node dysfunction, angina, heart failure, hypertension, atrial fibrillation, atrial flutter, dilated cardiomyopathy, idiopathic cardiomyopathy, myocardial infarction, coronary artery 30 disease, coronary artery spasm, or arrhythmia). In conjunction with such treatment, pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype

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and that individual's response to a foreign compound or drug) may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, a physician or clinician may consider applying 5 knowledge obtained in relevant pharmacogenomics studies in determining whether to administer a PCIP molecule or PCIP modulator as well as tailoring the dosage and/or therapeutic regimen of treatment with a PCIP molecule or PCIP modulator.

Pharmacogenomics deals with clinically significant hereditary variations in the response to drugs due to altered drug disposition and abnormal action in affected 10 persons. See, for example, Eichelbaum, M. *et al.* (1996) *Clin. Exp. Pharmacol. Physiol.* 23(10-11):983-985 and Linder, M.W. *et al.* (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic 15 conditions transmitted as a single factor altering the way drugs act on the body (altered drug action) or genetic conditions transmitted as single factors altering the way the body acts on drugs (altered drug metabolism). These pharmacogenetic conditions can occur either as rare genetic defects or as naturally-occurring polymorphisms. For example, glucose-6-phosphate dehydrogenase deficiency (G6PD) is a common inherited 20 enzymopathy in which the main clinical complication is haemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

One pharmacogenomics approach to identifying genes that predict drug response, known as "a genome-wide association", relies primarily on a high-resolution map of the human genome consisting of already known gene-related markers (*e.g.*, a "biallelic" gene marker map which consists of 60,000-100,000 polymorphic or variable 25 sites on the human genome, each of which has two variants.) Such a high-resolution genetic map can be compared to a map of the genome of each of a statistically significant number of patients taking part in a Phase II/III drug trial to identify markers associated with a particular observed drug response or side effect. Alternatively, such a high resolution map can be generated from a combination of some ten-million known 30 single nucleotide polymorphisms (SNPs) in the human genome. As used herein, a "SNP" is a common alteration that occurs in a single nucleotide base in a stretch of

DNA. For example, a SNP may occur once per every 1000 bases of DNA. A SNP may be involved in a disease process, however, the vast majority may not be disease-associated. Given a genetic map based on the occurrence of such SNPs, individuals can be grouped into genetic categories depending on a particular pattern of SNPs in their individual genome. In such a manner, treatment regimens can be tailored to groups of genetically similar individuals, taking into account traits that may be common among such genetically similar individuals.

Alternatively, a method termed the "candidate gene approach", can be utilized to identify genes that predict drug response. According to this method, if a gene that encodes a drugs target is known (*e.g.*, a PCIP protein of the present invention), all common variants of that gene can be fairly easily identified in the population and it can be determined if having one version of the gene versus another is associated with a particular drug response.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, PM show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

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Alternatively, a method termed the "gene expression profiling", can be utilized to identify genes that predict drug response. For example, the gene expression of an animal dosed with a drug (e.g., a PCIP molecule or PCIP modulator of the present invention) can give an indication whether gene pathways related to toxicity have been turned on.

Information generated from more than one of the above pharmacogenomics approaches can be used to determine appropriate dosage and treatment regimens for prophylactic or therapeutic treatment an individual. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a PCIP molecule or PCIP modulator, such as a modulator identified by one of the exemplary screening assays described herein.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application, as well as the Figures and the Sequence Listing are incorporated herein by reference.

EXAMPLES

The following materials and methods were used in the Examples.

Strains, plasmids, bait cDNAs, and general microbiological techniques

Basic yeast strains (HF7c, Y187), bait (pGBT9) and fish (pACT2) plasmids used in this work were purchased from Clontech (Palo Alto, CA). cDNAs encoding rat Kv4.3, Kv4.2, and Kv1.1, were provided by Wyeth-Ayerst Research (865 Ridge Rd., Monmouth Junction, NJ 08852). Standard yeast media including synthetic complete medium lacking L-leucine, L-tryptophan, and L-histidine were prepared and yeast genetic manipulations were performed as described (Sherman (1991) *Meth. Enzymol.* 194:3-21). Yeast transformations were performed using standard protocols (Gietz *et al.* (1992) *Nucleic Acids Res.* 20:1425; Ito *et al* (1983) *J. Bacteriol.* 153:163-168). Plasmid

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DNAs were isolated from yeast strains by a standard method (Hoffman and Winston (1987) *Gene* 57:267-272).

Bait and Yeast Strain Construction

5 The first 180 amino acids of rKv4.3 (described in Serdio P. *et al.* (1996) *J. Neurophys* 75:2174-2179) were amplified by PCR and cloned in frame into pGBT9 resulting in plasmid pFWA2, (hereinafter "bait"). This bait was transformed into the two-hybrid screening strain HF7c and tested for expression and self-activation. The bait was validated for expression by Western blotting. The rKv4.3 bait did not self-activate
10 in the presence of 10 mM 3-amino-1,2,3-Triazole (3-AT).

Library construction

Rat mid brain tissue was provided by Wyeth-Ayerst Research (Monmouth Junction, NJ). Total cellular RNA was extracted from the tissues using standard
15 techniques (Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, (1989)). mRNA was prepared using a Poly-A Spin mRNA Isolation Kit from New England Biolabs (Beverly, MA). cDNA from the mRNA sample was synthesized using a cDNA Synthesis Kit from Stratagene (La
20 Jolla, CA) and ligated into pACT2's EcoRI and XhoI sites, giving rise to a two-hybrid library.

Two-Hybrid Screening

Two-hybrid screens were carried out essentially as described in Bartel, P. *et al.*
25 (1993) "Using the Two-Hybrid System to Detect Polypeptide-Polypeptide Interactions" in *Cellular Interactions in Development: A Practical Approach*, Hartley, D.A. ed. Oxford University Press, Oxford, pp. 153-179, with a bait-library pair of rkv4.3 bait-rat mid brain library. A filter disk beta-galactosidase (beta-gal) assay was performed essentially as previously described (Brill *et al.* (1994) *Mol. Biol. Cell.* 5:297-312). Clones that were
30 positive for both reporter gene activity (His and beta-galactosidase) were scored and fish, plasmids were isolated from yeast, transformed into *E. coli* strain KC8, DNA

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plasmids were purified and the resulting plasmids were sequenced by conventional methods (Sanger F. *et al.* (1977) *PNAS*, 74: 5463-67).

Specificity test

5 Positive interactor clones were subjected to a binding specificity test where they
were exposed to a panel of related and unrelated baits by a mating scheme previously
described (Finley R.L. Jr. *et al.* (1994) *PNAS*, 91(26):12980-12984). Briefly, positive
fish plasmids were transformed into Y187 and the panel of baits were transformed into
HF7c. Transformed fish and bait cells were streaked out as stripes on selective medium
10 plates, mated on YPAD plates, and tested for reporter gene activity.

Analysis

PCIP nucleotides were analyzed for nucleic acid hits by the BLASTN 1.4.8MP
program (Altschul *et al.* (1990) Basic Local Alignment Search Tool. *J. Mol. Biol.* 215:
15 403-410). PCIP proteins were analyzed for polypeptide hits by the BLASTP 1.4.9MP
program.

EXAMPLE 1: IDENTIFICATION OF RAT PCIP cDNAs

The Kv4.3 gene coding sequence (coding for the first 180 amino acids) was
20 amplified by PCR and cloned into pGBT9 creating a GAL4 DNA-binding domain-
Kv4.3(1-180) gene fusion (plasmid pFWA2). HF7c was transformed with this
construct. The resulting strain grew on synthetic complete medium lacking L-
tryptophan but not on synthetic complete medium lacking L-tryptophan and L-histidine
in the presence of 10mM 3-AT demonstrating that the {GAL4 DNA-binding domain}-
25 {vKv4.3(1-180)} gene fusion does not have intrinsic transcriptional activation activity
higher than the threshold allowed by 10mM 3-AT.

In this example, a yeast two-hybrid assay was performed in which a plasmid
containing a {GAL4 DNA-binding domain}-{rKv4.3(1-180)} gene fusion was
introduced into the yeast two-hybrid screening strain HF7c described above. HF7c was
30 then transformed with the rat mid brain two-hybrid library. Approximately six million
transformants were obtained and plated in selection medium. Colonies that grew in the

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selection medium and expressed the beta-galactosidase reporter gene were further characterized and subjected to retransformation and specificity assays. The retransformation and specificity tests yielded three PCIP clones (rat 1v, 8t, and 9qm) that were able to bind to the Kv4.3 polypeptide.

5 The full length sequences for the rat 1v gene, and partial sequences for 8t and 9q genes were derived as follows. The partial rat PCIP sequences were used to prepare probes, which were then used to screen, for example, rat mid brain cDNA libraries. Positive clones were identified, amplified and sequenced using standard techniques, to obtain the full length sequence. Additionally, a rapid amplification of the existing rat
10 PCIP cDNA ends (using for example, 5' RACE, by Gibco, BRL) was used to complete the 5' end of the transcript.

EXAMPLE 2: IDENTIFICATION OF HUMAN 1v cDNA

To obtain the human 1v nucleic acid molecule, a cDNA library made from a
15 human hippocampus (Clontech, Palo Alto, CA) was screened under low stringency conditions as follows: Prehybridization for 4 hours at 42°C in Clontech Express Hyb solution, followed by overnight hybridization at 42°C. The probe used was a PCR-generated fragment including nucleotides 49-711 of the rat sequence labeled with ³²P dCTP. The filters were washed 6 times in 2XSSC/0.1% SDS at 55°C. The same
20 conditions were used for secondary screening of the positive isolates. Clones thus obtained were sequenced using an ABI automated DNA Sequencing system, and compared to the rat sequences shown in SEQ ID NO:3 as well as to known sequences from the GenBank database. The largest clone from the library screen was subsequently subcloned into pBS-KS+ (Stratagene, La Jolla, CA) for sequence verification. The 515
25 base pair clone was determined to represent the human homolog of the 1v gene, encompassing 211 base pairs of 5' UTR and a 304 base pair coding region. To generate the full-length cDNA, 3' RACE was used according to the manufacturers instructions (Clontech Advantage PCR kit).

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EXAMPLE 3: ISOLATION AND CHARACTERIZATION OF 1V SPLICE VARIANTS

The mouse 1v shown in SEQ ID NO:5 and the rat 1vl splice variant shown in SEQ ID NO:7 was isolated using a two-hybrid assay as described in Example 1. The
5 mouse 1vl splice variant shown in SEQ ID NO: 7 was isolated by screening a mouse brain cDNA library, and the rat 1vn splice variant shown in SEQ ID NO:11 was isolated by BLAST searching.

**EXAMPLE 4: ISOLATION AND IDENTIFICATION OF 9Q AND OTHER
10 PCIPs**

Rat 9ql (SEQ ID NO: 15) was isolated by database mining, rat 9qm (SEQ ID NO: 21) was isolated by a two-hybrid assay, and rat 9qc (SEQ ID NO:27) was identified by database mining. Human 9ql (SEQ ID NO: 13), and human 9qs (SEQ ID NO: 23) were identified as described in Example 2. Mouse 9ql (SEQ ID NO:17),
15 monkey 9qs (SEQ ID NO:25), human p193 (SEQ ID NO:39), rat p19 (SEQ ID NO:33), and mouse p19 (SEQ ID NO:35) were identified by database mining. Rat 8t (SEQ ID NO:29) was identified using a two-hybrid assay. The sequence of W28559 (SEQ ID NO:37) was identified by database mining and sequencing of the identified EST with Genbank Accession Number AI352454. The protein sequence was found to contain a
20 41 amino acid region with strong homology to 1v, 9ql, and p19 (see alignment in Figure 25). However, downstream of this homologous region the sequence diverges from that of the PCIP family. This sequence could represent a gene which possesses a 41 amino acid domain with homology to a similar domain found in the PCIP family members.

The human genomic 9q sequence (SEQ ID NOs:46 and 47) was isolated by
25 screening a BAC genomic DNA library (Research Genetics) using primers which were designed based on the sequence of the human 9qm cDNA. Two positive clones were identified (448O2 and 721I17) and sequenced.

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**EXAMPLE 5: EXPRESSION OF 1V, 8T, AND 9Q mRNA IN RAT
TISSUES**

Rat and mouse multiple tissue Northern blots (Clontech) were probed with a [³²P]-labeled cDNA probe directed at the 5'-untranslated and 5'- coding region of the rat 1v sequence (nucleotides 35-124; SEQ ID NO:3) (this probe is specific for rat 1v and rat 1vl), the 5' coding region of the 8t sequence (nucleotides 1-88; SEQ ID NO:29) (this probe is specific for 8t), or the 5' end of the rat 9qm sequence (nucleotides 1-195; SEQ ID NO:21) (this probe is specific for all 9q isoforms, besides 8t). Blots were hybridize using standard techniques. Northern blots hybridized with the rat 1v probe revealed a single band at 2.3kb only in the lane containing brain RNA, suggesting that 1v expression is brain specific. Northern blots probed with the rat 8t probe revealed a major band at 2.4kb. The rat 8t band was most intense in the lane containing heart RNA and there was also a weaker band in the lane containing brain RNA. Northern blots hybridized with the 9q cDNA probe revealed a major band at 2.5kb and a minor band at over 4kb with predominant expression in brain and heart. The minor band may represent incompletely spliced or processed 9q mRNA. The results from the northern blots further indicated that p19 is expressed predominantly in the heart.

EXAMPLE 6: EXPRESSION OF 1V, 8T, AND 9Q IN BRAIN

Expression of the rat 1v and 8t/9q genes in the brain was examined by *in situ* hybridization histochemistry (ISHH) using [³⁵S]-labeled cRNA probes and a hybridization procedure identical to that described in Rhodes *et al.* (1996) J. Neurosci., 16:4846-4860. Templates for preparing the cRNA probes were generated by standard PCR methods. Briefly, oligonucleotide primers were designed to amplify a fragment of the 3'- or 5'-untranslated region of the target cDNA and in addition, add the promoter recognition sequences for T7 and T3 polymerase. Thus, to generate a 300 nucleotide probe directed at the 3'-untranslated region of the 1v mRNA, we used the following primers:

5-TAATACGACTCACTATAAGGGACTGGCCATCCTGCTCTCAG-3 (T7, forward, sense; SEQ ID NO:42)

- 5-ATTAACCCTCACTAAAGGGACACTACTGTTAAGCTCAAG-3 (T3, reverse, antisense; SEQ ID NO:43). The underlined bases correspond to the T7 and T3 promoter sequences. To generate a probe directed at a 325 bp region of 3'-untranslated sequence shared by the 8t and 9q mRNAs, the following primers were used:
- 5 5-TAATACGACTCACTATAAGGGCACCTCCCCCTCCGGCTGTT-3 (T7, forward, sense; SEQ ID NO:44)
- 5-ATTAACCCTCACTAAAGGGAGAGCAGCAGCATGGCAGGGT-3 (T3, reverse, antisense; SEQ ID NO:45).

Autoradiograms of rat brain tissue sections processed for ISHH localization of 1v or 8t/9q mRNA expression revealed that 1v mRNA is expressed widely in brain in a pattern consistent with labeling of neurons as opposed to glial or endothelial cells. 1v mRNA is highly expressed in cortical, hippocampal, and striatal interneurons, the reticular nucleus of the thalamus, the medial habenula, and in cerebellar granule cells. 1v mRNA is expressed at moderate levels in midbrain nuclei including the substantia nigra and superior colliculus, in several other thalamic nuclei, and in the medial septal and diagonal band nuclei of the basal forebrain.

Because the probe used to analyze the expression of 8t and 9q hybridizes to a region of the 3-untranslated region that is identical in the 8t and 9q mRNAs, this probe generates a composite image that reveals that 8t/9q mRNA is expressed widely in brain in a pattern that partly overlaps with that for 1v as described above. However, 8t/9q mRNA is highly expressed in the striatum, hippocampal formation, cerebellar granule cells, and neocortex. 8t/9q mRNA is expressed at moderate levels in the midbrain, thalamus, and brainstem. In many of these areas, 8t/9q mRNA appears to be concentrated in interneurons in addition to principal cells, and in all regions 8t/9q expression appears to be concentrated in neurons as opposed to glial cells.

Single- and double-label immunohistochemistry revealed that the PCIP and Kv4 polypeptides are precisely colocalized in many of the cell types and brain regions where PCIP and Kv4 mRNAs are coexpressed. For example, 9qm colocalized with Kv4.2 in the somata and dendrites of hippocampal granule and pyramidal cells, neurons in the medial habenular nucleus and in cerebellar basket cells, while 1v colocalized with Kv4.3 in layer II neurons of posterior cingulate cortex, hippocampal interneurons, and in a

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subset of cerebellar granule cells. Immunoprecipitation analyses indicated that 1v and 9qm are coassociated with Kv4 α -subunits in rat brain membranes.

**EXAMPLE 7: CO-ASSOCIATION OF PCIPs AND Kv4 CHANNELS
IN COS AND CHO CELLS**

COS1 and CHO cells were transiently transfected with individual PCIPs (KChIP1, KChIP2, KChIP3) alone or together with Kv4.2 or Kv4.3 using the lipofectamine plus procedure essentially as described by the manufacturer (Boehringer Mannheim). Forty-eight hours after the transfection, cells were washed, fixed, and 10 processed for immunofluorescent visualization as described previously (Bekele-Arcuri *et al.* (1996) *Neuropharmacology*, 35:851-865). Affinity-purified rabbit polyclonal or mouse monoclonal antibodies to the Kv4 channel or the PCIP protein were used for immunofluorescent detection of the target proteins.

When expressed alone, the PCIPs were diffusely distributed throughout the 15 cytoplasm of COS-1 and CHO cells, as would be expected for cytoplasmic proteins. In contrast, when expressed alone, the Kv4.2 and Kv4.3 polypeptides were concentrated within the perinuclear ER and Golgi compartments, with some immunoreactivity concentrated in the outer margins of the cell. When the PCIPs were coexpressed with Kv4 α -subunits, the characteristic diffuse PCIP distribution changed dramatically, such 20 that the PCIPs precisely colocalized with the Kv4 α -subunits. This redistribution of the PCIPs did not occur when they were coexpressed with the Kv1.4 α -subunit, indicating that altered PCIP localization is not a consequence of overexpression and that these PCIPs associate specifically with Kv4-family α -subunits.

To verify that the PCIP and Kv4 polypeptides are tightly associated and not 25 simply colocalized in co-transfected cells, reciprocal immunoprecipitation analyses were performed using the PCIP and channel-specific antibodies described above. All three PCIP polypeptides coassociated with Kv4 α -subunits in cotransfected cells, as evidenced by the ability of anti-Kv4.2 and anti-Kv4.3 antibodies to immunoprecipitate the KChIP1, KChIP2, and KChIP3 proteins from lysates prepared from cotransfected 30 cells, and by the ability of anti-PCIP antibodies to immunoprecipitate Kv4.2 and Kv4.3

α -subunits from these same lysates. The cells were lysed in buffer containing detergent and protease inhibitors, and prepared for immunoprecipitation reactions essentially as described previously (Nakahira *et al.* (1996) J. Biol. Chem., 271:7084-7089).

Immunoprecipitations were performed as described in Nakahira *et al.* (1996) J. Biol. 5 Chem., 271:7084-7089 and in Harlow E. and Lane, D., Antibodies:A Laboratory Manual, Cold Spring Harbor Laboratory, c1988. The products resulting from the immunoprecipitation were size fractionated by SDS-PAGE and transferred to nitrocellulose filters using standard procedures.

To confirm that the cytoplasmic N-terminus of Kv4 channels is sufficient for the 10 interaction with the PCIPs KChIP1 or KChIP2 were co-expressed with a Kv4.3 mutant (Kv4.3 Δ C) that lacks the entire 219 amino acid cytoplasmic C-terminal tail. In transiently transfected COS-1 cells, the Kv4.3 Δ C mutant was extensively trapped within the perinuclear ER and Golgi: little or no staining was observed at the outer margins of the cell. Nonetheless, KChIP1 and KChIP2 precisely colocalized with Kv4.3 Δ C in 15 cotransfected cells, and moreover, Kv4.3 Δ C was efficiently coimmunoprecipitated by PCIP antibodies, indicating that the interaction of these PCIPs with Kv4 α -subunits does not require the cytoplasmic C-terminus of the channel.

EXAMPLE 8: CO-ASSOCIATION OF PCIPs AND Kv4 CHANNELS IN
20 NATIVE TISSUES

To determine whether PCIPs colocalize and co-associate with Kv4 subunits in native tissues, Kv4- and PCIP-specific antibodies were used for single and double-label immunohistochemical analyses and for reciprocal coimmunoprecipitation analyses of rat brain membranes. Immunohistochemical staining of rat brain sections indicated that 25 KChIP1 and KChIP2 colocalize with Kv4.2 and Kv4.3 in a region and cell type-specific manner. For example, KChIP1 colocalized with Kv4.3 in hippocampal interneurons, cerebellar granule cells, and cerebellar glomeruli, a specialized synaptic arrangement between the dendrites of cerebellar basket and golgi cells and mossy fiber terminals. KChIP2 colocalized with Kv4.3 and Kv4.2 in the dendrites of granule cells in the 30 dentate gyrus, in the apical and basal dendrites of hippocampal and neocortical

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pyramidal cells, and in several subcortical structures including the striatum and superior colliculus. Co-immunoprecipitation analyses performed using synaptic membranes prepared from whole rat brain revealed that the PCIPs (KChIPs 1, 2, and 3) are tightly associated with Kv4.2 and Kv4.3 in brain K⁺ channel complexes. Anti-PCIP antibodies immunoprecipitated Kv4.2 and Kv4.3 from brain membranes, and anti-Kv4.2 and Kv4.3 antibodies immunoprecipitated the PCIPs. None of the PCIP polypeptides were immunoprecipitated by anti-Kv2.1 antibodies, indicating that the association of these PCIPs with brain Kv channels may be specific for Kv4 α -subunits. Taken together, these anatomical and biochemical analyses indicate that these PCIPs are integral components of native Kv4 channel complexes.

EXAMPLE 9:**PCIPs ARE CACIUM BINDING PROTEINS**

To determine whether KChIPs 1, 2, and 3 bind Ca²⁺, GST-fusion proteins were generated for each PCIP and the ability of the GST-PCIP proteins, as well as the recombinant PCIP polypeptides enzymatically cleaved from GST, to bind ⁴⁵Ca²⁺ was examined using a filter overlay assay (described in, for example, Kobayashi *et al.* (1993) *Biochem. Biophys. Res. Commun.* 189(1):511-7). All three PCIP polypeptides, but not an unrelated GST-fusion protein, display strong ⁴⁵Ca²⁺ binding in this assay. Moreover, all three PCIP polypeptides display a Ca²⁺-dependent mobility shift on SDS-PAGE, indicating that like the other members of this family, KChIPs 1, 2 and 3 are in fact Ca²⁺-binding proteins (Kobayashi *et al.* (1993) *supra*; Buxbaum *et al.* Nef (1996) *Neuron-specific calcium sensors (the NCS-1 subfamily)*. In: Celio MR (ed) *Guidebook to the calcium-binding proteins*. Oxford University Press, New York, pp94-98; Buxbaum J.D., *et al.* (1998) *Nature Med.* 4(10):1177-81.

**EXAMPLE 10: ELECTROPHYSIOLOGICAL CHARACTERIZATION
OF PCIPs**

Because PCIPs, e.g., KChIP1 (1v), KChIP2 (9ql), and KChIP3 (p19), colocalize and coassociate with Kv4 α -subunits in brain, another critical question was to determine whether these PCIPs alter the conductance properties of Kv4 channels. To address this issue, Kv4.2 and Kv4.3 were expressed alone and in combination with individual PCIPs. CHO cells were transiently-transfected with cDNA using the DOTAP lipofection method as described by the manufacturer (Boehringer Mannheim, Inc.). Transfected cells were identified by cotransfected enhanced GFP along with the genes of interest and subsequently determining if the cells contained green GFP fluorescence. Currents in CHO cells were measured using the patch-clamp technique (Hamill *et al.* 1981. Pfluegers Arch. 391: 85-100).

Transient transfection of the rat Kv4.2 α -subunit in CHO cells resulted in expression of a typical A-type K⁺ conductance. Coexpression of Kv4.2 with KChIP1 revealed several dramatic effects of KChIP1 on the channel (Figure 41 and Table 1). First, the amplitude of the Kv4.2 current increased approximately 7.5 fold in the presence of KChIP1 (amplitude of Kv4.2 alone = 0.60 +/- 0.096 nA/cell; Kv4.2 + KChIP1 = 4.5 +/- 0.55 nA/cell). When converted into current density by correcting for cell capacitance, a measure of cell surface membrane area, the Kv4.2 current density increased 12 fold with coexpression of KChIP1 (Kv4.2 alone = 25.5 +/- 3.2 pA/pF; Kv4.2 + KChIP1 = 306.9 +/- 57.9 pA/pF), indicating that KChIPs promote and/or stabilize Kv4.2 surface expression. Together with this increase in current density, a dramatic leftward shift in the threshold for activation of Kv4.2 currents was observed in cells expressing Kv4.2 and KChIP1 (activation V1/2 for Kv4.2 alone = 20.8 +/- 7.0mV, Kv4.2 + KChIP1 = -12.1 +/- 1.4 mV). Finally, the kinetics of Kv4.2 inactivation slowed considerably when Kv4.2 was coexpressed with KChIP1 (inactivation time constant of Kv4.2 alone = 28.2 +/- 2.6 ms; Kv4.2 + KChIP1 = 104.1 +/- 10.4 ms), while channels recovered from inactivation much more rapidly in cells expressing both Kv4.2 and KChIP1 (recovery tau = 53.6 +/- 7.6 ms) versus cells expressing Kv4.2 alone (recovery tau = 272.2 +/- 26.1 ms).

- KChIPs1, 2 and 3 have distinct N-termini but share considerable amino acid identity within the C-terminal "core" domain. Despite their distinct N-termini, the effects of KChIP2 and KChIP3 on Kv4.2 current density and kinetics were strikingly similar to those produced by KChIP1 (Table1). Thus to confirm that the conserved C-terminal core domain, which contains all three EF-hands, is sufficient to modulate Kv4 current density and kinetics, N-terminal truncation mutants of KChIP1 and KChIP2 were prepared. The KChIP1 Δ N2-31 and KChIP2 Δ N2-67 mutants truncated KChIP1 and KChIP2, respectively, to the C-terminal 185 amino acid core sequence.
- Coexpression of KChIP1 Δ N2-31 or KChIP2 Δ N2-67 with Kv4.2 in CHO cells produced changes in Kv4.2 current density and kinetics that were indistinguishable from the effects produced by full-length KChIP1 or KChIP2 (Table1).

To investigate whether the modulatory effects of these KChIPs are specific for Kv4 channels, KChIP1 was coexpressed with Kv1.4 and Kv2.1 in *Xenopus* oocytes. *Xenopus* oocytes were injected with 1-3 ng/oocyte of cRNA which was prepared using standard in vitro transcription techniques (Sambrook *et al.* 1989. Molecular Cloning: a laboratory manual, Cold Spring Harbor Press). Currents in oocytes were measured with a two-electrode voltage clamp. KChIP1 did not appear to have any effect on Kv1.4 or Kv2.1 currents (Table2), indicating that these functional effects may be specific for Kv4 channels. As a final control for the KChIP effects and to verify that the KChIPs' effects on Kv4 currents are independent of expression system, the above kinetic analyses were repeated after expressing Kv4.3 and KChIP mRNAs in *Xenopus* oocytes. The effects KChIP1 on Kv4.3 in the oocyte system were strikingly similar to those on Kv4.2 in CHO cells (Table1).

Since these KChIPs bind Ca²⁺, another important question is to determine whether the effects of KChIP1 on Kv4.2 currents are Ca²⁺-dependent. This question was addressed indirectly by introducing point mutations within each of KChIP1's EF-hand domains: one mutant has point mutations in the first two EF hands (D₁₉₉ to A, G₁₀₄ to A, D₁₃₅ to A, and G₁₄₀ to A) and the other one has point mutations in all three EF hands (D₁₉₉ to A, G₁₀₄ to A, D₁₃₅ to A, G₁₄₀ to A, D₁₈₃ to A, and G₁₈₈ to A). These mutations substituted alanine for the two most highly conserved amino acids within the EF-hand consensus (Figure 25; Linse, S. and Forsen, S. (1995) Determinants that govern high-

- 130 -

- affinity Calcium binding. In Means, S. (Ed.)Advances in second messenger and phosphoprotein research. New York, Ravens Press,. 30:89-150). Coexpression of this KChIP1 triple EF-hand mutant with Kv4.2 or Kv4.3 in COS cells indicated that this mutant colocalizes and is efficiently coimmunoprecipitated with Kv4 α -subunits in
- 5 COS-1 cells. However, these EF-hand point mutations completely eliminated the effects of KChIP1 on Kv4.2 kinetics (Table1). Taken together, these results indicate that the binding interaction between KChIP1 and Kv4.2 is Ca²⁺ independent, while modulation of Kv4.2 kinetics by KChIP1 is either Ca²⁺-dependent or sensitive to structural changes induced by point mutations within the EF-hand domains.

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TABLE 1

Functional effect of KchlPs on Kv4 channels

Current Parameter	rKv4.2 + vector	rKv4.2 + KchlP1	rKv4.2 + KchlP1 ΔN2-31	rKv4.2 + KchlP2	rKv4.2 + KchlP2 ΔN2-67	rKv4.2 + KchlP3	rKv4.3	rKv4.3 + KchlP1
Peak Current	0.60*	4.5*	6.0*	3.3*	5.8*	3.5*	7.7μA	18.1μA*
(nA/cell at 50 MV)	+0.096	+0.055	+1.1	+0.45	+1.1	+0.99	+2.6	+3.8
Peak Current Density	25.5	306.9*	407.2*	196.6*	202.6*	161.7*	---	---
(pA/pF at 50 mV)	+3.2	+57.9	+104.8	+26.6	+27.5	+21.8		
Inactivation time constant	28.2	104.1	129.2	95.1*	109.5*	67.2*	56.3	135.0
(ms, at 50 mV)	+2.6	+10.4	+14.2	+8.3	+9.6	+14.1	+6.6	+15.1
Recovery from Inactivation Time constant	272.2	53.6*	98.1*	49.5*	36.1*	126.1*	327.0	34.5*

* Significantly different from control.

TABLE 2

Functional effects of KChIPs on other Kv channels

Current Parameter	Oocytes		Oocytes	
	H Kv1.4	h Kv1.4 + 1v	H Kv2.1	H Kv2.1 + 1v
Peak Current	8.3	6.5	3.7	2.9
(μ A/cell at 50 MV)	\pm 2.0	\pm 0.64	\pm 0.48	\pm 0.37
Inactivation time constant (ms, at 50 mV)	53.2	58.2	1.9 s	1.7 s
Recovery from Inactivation time constant (sec, at -80 mV)	\pm 2.8	\pm 6.6	\pm 0.079	0.078
Activation $V_{1/2}$ (mV)	-21.0	-20.9	12.0	12.4
Steady-state Inactivation $V_{1/2}$ (mV)	-48.1	-47.5	-25.3	-23.9

5 EXAMPLE 11: EFFECTS OF KChIP1 ON SURFACE EXPRESSION OF KV4- α SUBUNITS IN COS-1 CELLS

To examine the ability of KChIP1 to enhance the surface expression of Kv4 channels, the ability of KChIP1 to promote the formation of surface co-clusters of Kv4 channels and PSD-95 was monitored. PSD-95 is used to facilitate the visualization of 10 the complex.

To facilitate the interaction between Kv4.3 and PSD-95, a chimeric Kv4.3 subunit (Kv4.3ch) was generated in which the C-terminal 10 amino acids from rKv1.4

- (SNAKAVETDV, SEQ ID NO:73) were appended to the C-terminus of Kv4.3. The C-terminal 10 amino acids from rKv1.4 were used because they associate with PSD-95 and confer the ability to associate with PSD-95 to the Kv4.3 protein when fused to the Kv4.3 C-terminus. Expression of Kv4.3ch in COS-1 cells revealed that the Kv4.3ch
- 5 polypeptide was trapped in the perinuclear cytoplasm, with minimal detectable Kv4.3ch immunoreactivity at the outer margins of the cell. When Kv4.3ch was co-expressed with PSD-95, PSD-95 became trapped in the perinuclear cytoplasm and co-localized with Kv4.3ch. However, when KChIP1 was co-expressed with Kv4.3ch and PSD-95, large plaque-like surface co-clusters of Kv4.3ch, KChIP1 and PSD-95 were observed.
- 10 Triple-label immunofluorescence confirmed that these surface clusters contain all three polypeptides, and reciprocal co-immunoprecipitation analyses indicated that the three polypeptides are co-associated in these surface clusters. Control experiments indicated that KChIP1 does not interact with PSD-95 alone, and does not co-localize with Kv1.4 and PSD-95 in surface clusters. Taken together, these data indicate that KChIP1 may
- 15 promote the transit of the Kv4.3 subunits to the cell surface.

EXAMPLE 12: CHARACTERIZATION OF THE PCIP PROTEINS

In this example, the amino acid sequences of the PCIP proteins were compared to amino acid sequences of known proteins and various motifs were identified.

- 20 The 1v polypeptide, the amino acid sequence of which is shown in SEQ ID NO:3 is a novel polypeptide which includes 216 amino acid residues. Domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York), were identified by sequence alignment (see
- 25 Figure 21).

- The 8t polypeptide, the amino acid sequence of which is shown in SEQ ID NO:30 is a novel polypeptide which includes 225 amino acid residues. Calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York), were identified by sequence alignment (see Figure 21).

The 9q polypeptide is a novel polypeptide which includes calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York (see Figure 21).

5 The p19 polypeptide is a novel polypeptide which includes calcium binding domains that are putatively involved in calcium binding (Linse, S. and Forsen, S. (1995) *Advances in Second Messenger and Phosphoprotein Research* 30, Chapter 3, p89-151, edited by Means, AR., Raven Press, Ltd., New York (see Figure 21).

A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the
10 nucleotide sequence of rat 1vl revealed that the rat 1vl is similar to the rat cDNA clone RMUAH89 (Accession Number AA849706). The rat 1 vl nucleic acid molecule is 98% identical to the rat cDNA clone RMUAH89 (Accession Number AA849706) over nucleotides 1063 to1488.

A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the
15 nucleotide sequence of human 9ql revealed that the human 9ql is similar to the human cDNA clone 1309405 (Accession Number AA757119). The human 9 ql nucleic acid molecule is 98% identical to the human cDNA clone 1309405 (Accession Number AA757119) over nucleotides 937 to1405.

A BLASTN 2.0.7 search (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the
20 nucleotide sequence of mouse P19 revealed that the mouse P19 is similar to the Mus musculus cDNA clone MNCb-7005 (Accession Number AU035979). The mouse P19 nucleic acid molecule is 98% identical to the Mus musculus cDNA clone MNCb-7005 (Accession Number AU035979) over nucleotides 1 to 583.

25 **EXAMPLE 13: EXPRESSION OF RECOMBINANT PCIP PROTEINS
IN BACTERIAL CELLS**

In this example, PCIP is expressed as a recombinant glutathione-S-transferase (GST) fusion polypeptide in *E. coli* and the fusion polypeptide is isolated and characterized. Specifically, PCIP is fused to GST and this fusion polypeptide is
30 expressed in *E. coli*, e.g., strain BI21. Expression of the GST-PCIP fusion protein in BI21 is induced with IPTG. The recombinant fusion polypeptide is purified from crude

bacterial lysates of the induced BI21 strain by affinity chromatography on glutathione beads. Using polyacrylamide gel electrophoretic analysis of the polypeptide purified from the bacterial lysates, the molecular weight of the resultant fusion polypeptide is determined.

- 5 Rat 1v and 9ql were cloned into pGEX-6p-2 (Pharmacia). The resulting recombinant fusion proteins were expressed in *E. coli* cells and purified following art known methods (described in, for example, *Current Protocols in Molecular Biology*, eds. Ausubel *et al.* John Wiley & Sons: 1992). The identities of the purified proteins were verified by western blot analysis using antibodies raised against peptide epitopes of
10 rat 1v and 9ql.

**EXAMPLE 14: EXPRESSION OF RECOMBINANT PCIP PROTEINS
IN COS CELLS**

- To express the PCIP gene in COS cells, the pcDNA/Amp vector by Invitrogen
15 Corporation (San Diego, CA) is used. This vector contains an SV40 origin of replication, an ampicillin resistance gene, an *E. coli* replication origin, a CMV promoter followed by a polylinker region, and an SV40 intron and polyadenylation site. A DNA fragment encoding the entire PCIP protein and an HA tag (Wilson *et al.* (1984) *Cell* 37:767) or a FLAG tag fused in-frame to its 3' end of the fragment is cloned into the
20 polylinker region of the vector, thereby placing the expression of the recombinant protein under the control of the CMV promoter.

- To construct the plasmid, the PCIP DNA sequence is amplified by PCR using two primers. The 5' primer contains the restriction site of interest followed by approximately twenty nucleotides of the PCIP coding sequence starting from the
25 initiation codon; the 3' end sequence contains complementary sequences to the other restriction site of interest, a translation stop codon, the HA tag or FLAG tag and the last 20 nucleotides of the PCIP coding sequence. The PCR amplified fragment and the pcDNA/Amp vector are digested with the appropriate restriction enzymes and the vector is dephosphorylated using the CIAP enzyme (New England Biolabs, Beverly,
30 MA). Preferably the two restriction sites chosen are different so that the PCIP gene is inserted in the correct orientation. The ligation mixture is transformed into *E. coli* cells

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(strains HB101, DH5a, SURE, available from Stratagene Cloning Systems, La Jolla, CA, can be used), the transformed culture is plated on ampicillin media plates, and resistant colonies are selected. Plasmid DNA is isolated from transformants and examined by restriction analysis for the presence of the correct fragment.

- 5 COS cells are subsequently transfected with the PCIP-pcDNA/Amp plasmid DNA using the calcium phosphate or calcium chloride co-precipitation methods, DEAE-dextran-mediated transfection, lipofection, or electroporation. Other suitable methods for transfecting host cells can be found in Sambrook, J., Fritsh, E. F., and Maniatis, T. *Molecular Cloning: A Laboratory Manual*. 2nd, ed., Cold Spring Harbor Laboratory, 10 Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989. The expression of the PCIP polypeptide is detected by radiolabelling (35 S-methionine or 35 S-cysteine available from NEN, Boston, MA, can be used) and immunoprecipitation (Harlow, E. and Lane, D. *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1988) using an HA specific monoclonal antibody. Briefly, the 15 cells are labelled for 8 hours with 35 S-methionine (or 35 S-cysteine). The culture media are then collected and the cells are lysed using detergents (RIPA buffer, 150 mM NaCl, 1% NP-40, 0.1% SDS, 0.5% DOC, 50 mM Tris, pH 7.5). Both the cell lysate and the culture media are precipitated with an HA specific monoclonal antibody. Precipitated polypeptides are then analyzed by SDS-PAGE.
- 20 Alternatively, DNA containing the PCIP coding sequence is cloned directly into the polylinker of the pCDNA/Amp vector using the appropriate restriction sites. The resulting plasmid is transfected into COS cells in the manner described above, and the expression of the PCIP polypeptide is detected by radiolabelling and immunoprecipitation using a PCIP specific monoclonal antibody.
- 25 Rat 1v was cloned into the mammalian expression vector pRBG4. Transfections into COS cells were performed using LipofectAmine Plus (Gibco BRL) following the manufacturer's instructions. The expressed 1v protein was detected by immunocytochemistry and/or western blot analysis using antibodies raised against 1v in rabbits or mice.

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EXAMPLE 15: IDENTIFICATION AND CHARACTERIZATION OF HUMAN FULL LENGTH P19

The human full length p19 sequence was identified using RACE PCR. The sequence of p19 (also referred to as KChIP3) is shown in Figure 16. The amino acid 5 sequence of human p19 is 92% identical to the mouse p19 gene (SEQ ID NO:35).

TBLASTN searches using the protein sequence of human p19 revealed that human p19 is homologous to two sequences, Calsenilin (described in (1998) *Nature Medicine* 4: 1177-1181) and DREAM, a Ca²⁺-dependent regulator of prodynorphin and c-fos transcription (described in Carrion *et al.* (1999) *Nature* 398: 80-84). Human p19 is 10 100% identical at the nucleotide level to Calsenilin (but extends 3' to the published sequence) and 99% identical at the nucleotide level to DREAM.

The ability of p19 (as well as other PCIP family members) to co-localize with presenilin and act as transcription factors is determined using art known techniques such as northern blots, *in situ* hybridization, β-gal assays, DNA mobility assays (described in, 15 for example, Carrion *et al.* (1999) *Nature* 398:80) and DNA mobility supershift assays, using antibodies specific for KchIPs.

Other assays suitable for evaluating the association of PCIP family members with presenilins is co-immunoprecipitation (described in, for example, Buxbaum *et al.* (1998) *Nature Medicine* 4:1177).

20

EXAMPLE 16: IDENTIFICATION AND CHARACTERIZATION OF MONKEY KChIP4

In this example, the identification and characterization of the genes encoding monkey KChIP4a (jlkbd352e01t1) and alternatively spliced monkey KChIP4b 25 (jlkbb231c04t1), KChIP4c (jlkxa053c02), and KChIP4d (jlkx015b10) is described. TBLASTN searches in proprietary databases with the sequence of the known PCIP family members, lead to the identification of four clones jlkbb231c04t1, jlkbd352e01t1, jlkxa053c02, and jlkx015b10. The four monkey clones were obtained and sequenced.

The sequences of proprietary monkey clones jlkbb231c04t1 and jlkbd352e01t1 30 were found to correspond to alternately spliced variants of an additional PCIP family member, referred to herein as KChIP4. Clone jlkbb231c04t1 contains a 822bp deletion

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relative to jlkbd352e01t1 (presumably due to splicing out of an exon), resulting in the loss of the final EF hand domain. In clone jlkbd352e01t1, the final EF hand domain is preserved, and the C-terminus is highly homologous to that of PCIP family members 1v, 9ql, and p19. Overall identity in the homologous C-termini among KChIP4, 1v, 9ql, and 5 p19 ranged from 71%-80% at the amino acid level (alignments were performed using the CLUSTALW).

Monkey KChIP4c and KChIP4d were discovered by BLASTN search using monkey KChIP4a as a query for searching a proprietary database.

10 The nucleotide sequence of the monkey KChIP4a cDNA and the predicted amino acid sequence of the KChIP4a polypeptide are shown in Figure 23 and in SEQ ID NOs:48 and 49, respectively.

The nucleotide sequence of the monkey KChIP4b cDNA and the predicted amino acid sequence of the KChIP4b polypeptide are shown in Figure 24 and in SEQ ID NOs:50 and 51, respectively.

15 The nucleotide sequence of the monkey KChIP4c cDNA and the predicted amino acid sequence of the KChIP4c polypeptide are shown in Figure 35 and in SEQ ID NOs:69 and 70, respectively.

The nucleotide sequence of the monkey KChIP4d cDNA and the predicted amino acid sequence of the KChIP4d polypeptide are shown in Figure 36 and in SEQ ID 20 NOs:71 and 72, respectively.

Figure 37 depicts an alignment of the protein sequences of KChIP4a, KChIP4b, KChIP4c, and KChIP4d.

Rat KChIP4 is predominantly expressed in the brain, and weakly in the kidney, but not in the heart, brain, spleen, lung, liver, skeletal muscle or testes, as indicated by 25 northern blot experiments in which a northern blot purchased from Clontech was probed with a DNA fragment from the 3'-untranslated region of rat KChIP4.

EXAMPLE 17: IDENTIFICATION AND CHARACTERIZATION OF HUMAN AND RAT 33b07

30 In this example, the identification and characterization of the genes encoding rat and human 33b07 is described. Partial rat 33b07 (clone name 9o) was isolated as a

positive clone from the yeast two-hybrid screen described above, using rKv4.3N as bait. The full length rat 33b07 clone was identified by mining of proprietary databases.

The nucleotide sequence of the full length rat 33b07 cDNA and the predicted amino acid sequence of the rat 33b07 polypeptide are shown in Figure 26 and in SEQ ID NOs:52 and 53, respectively. The rat 33b07 cDNA encodes a protein having a molecular weight of approximately 44.7 kD and which is 407 amino acid residues in length.

Rat 33b07 binds rKv4.3N and rKv4.2N with slight preference for rKv4.2N in yeast 2-hybrid assays. In contrast, rat 33b07 does not bind rKv1.1N, indicating that the 10 rat 33b07-Kv4N interaction is specific.

Rat 33b07 is expressed predominantly in the brain as determined by northern blot analysis.

The human 33b07 ortholog (clone 106d5) was also identified by mining of proprietary databases. The nucleotide sequence of the full length human 33b07 cDNA and the predicted amino acid sequence of the human 33b07 polypeptide are shown in Figure 27 and in SEQ ID NOS:54 and 55, respectively. The human 33b07 cDNA encodes a protein having a molecular weight of approximately 45.1 kD and which is 414 amino acid residues in length.

Human 33b07 is 99% identical to the human KIAA0721 protein (GenBank Accession Number: AB018264) at the amino acid level. However, GenBank Accession Number: AB018264 does not have a functional annotation. Human 33b07 is also homologous to Testes-specific (Y-encoded) proteins (TSP(Y)s), SET, and Nucleosome Assembly Proteins (NAPs). The human 33b07 is 38% identical to human SET protein (GenBank Accession Number Q01105=U51924) over amino acids 204 to 337 and 46% identical over amino acids 334 to 387.

Human SET is also called HLA-DR associated protein II (PHAPII) (Hoppe-Seyler (1994) *Biol. Chem.* 375:113-126) and in some cases is associated with acute undifferentiated leukemia (AUL) as a result of a translocation event resulting in the formation of a SET-CAN fusion gene (Von Lindern M. et al. (1992) *Mol. Cell. Biol.* 12:3346-3355). An alternative spliced form of SET is also called Template Activating Factor-I alpha (TAF). TAF is found to be associated with myeloid leukemogenesis

(Nagata K. *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A.* 92 (10), 4279-4283). Human SET is also a potent protein inhibitor of phosphatase 2A (Adachi Y. *et al.* (1994) *J. Biol. Chem.* 269:2258-2262). NAPs may be involved in modulating chromatin formation and contribute to regulation of cell proliferation (Simon H.U. *et al.* (1994) *Biochem. J.* 297, 5 389-397).

Thus, due to its homology to the above identified proteins, 33b07 may function as a protein inhibitor of phosphatase, an oncogene, and/or a chromatin modulator. The homology of 33b07 to SET, a protein phosphatase inhibitor, is of particular interest. Many channels, in particular the Kv4 channels (with which 33b07 is associated), are 10 known to be regulated by phosphorylation by PKC and PKA ((1998) *J. Neuroscience* 18(10): 3521-3528; Am J Physiol 273: H1775-86 (1997)). Thus, 33b07 may modulate Kv4 activity by regulating the phosphorylation status of the potassium channel.

EXAMPLE 18: IDENTIFICATION AND CHARACTERIZATION OF
15 RAT 1p

In this example, the identification and characterization of the gene encoding rat 1p is described. Partial rat 1p was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait.

The nucleotide sequence of the partial length rat 1p cDNA and the predicted 20 amino acid sequence of the rat 1p polypeptide are shown in Figure 28 and in SEQ ID NOs:56 and 57, respectively. The rat 1p cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 267 amino acid residues in length.

Rat 1p binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast 25 two-hybrid assays. In contrast, 1p does not bind rKv1.1N, indicating that the 1p-Kv4N interaction is specific.

Rat 1p is predominantly expressed in the brain as determined by northern blot analysis.

A BLASTP 1.4 search, using a score of 100 and a word length of 3 (Altschul *et al.* (1990) *J. Mol. Biol.* 215:403) of the amino acid sequences of rat 1p revealed that rat 30 1p is similar to the human Restin (GenBank Accession Number P30622; also named cytoplasmic linker protein-170 alpha-2 (CLIP-170), M97501)). The rat 1p protein is

58% identical to the human Restin over amino acid residues 105 to 182, 55% identical to the human Restin over amino acid residues 115 to 186, 22% identical to the human Restin over amino acid residues 173 to 246, 22% identical to the human Restin over amino acid residues 169 to 218, and 58% identical to the human Restin over amino acid residues 217 to 228.

- 5 Restin is also named Reed-Sternberg intermediate filament associated protein. Reed-Sternberg cells are the tumoral cells diagnostic for Hodgkin's disease. It is suggested that Restin overexpression may be a contributing factor in the progression of Hodgkin's disease (Bilbe G. *et al.* (1992) *EMBO J.* 11: 2103-13) and Restin appears to
10 be an intermediate filament associated protein that links endocytic vesicles to microtubules (Pierre P. *et al.* (1992) *Cell* 70 (6), 887-900).

- 15 The cytoskeleton regulates the activity of potassium channels (see, for example, Honore E. *et al.* (1992) *EMBO J.* 11:2465-2471 and Levin G. *et al.* (1996) *J. Biol. Chem.* 271:29321-29328), as well as the activity of other channels, e.g., Ca⁺⁺ channels (Johnson B.D. *et al.* (1993) *Neuron* 10:797-804); or Na⁺ channels (Fukuda J. *et al.* (1981) *Nature* 294:82-85).

20 Accordingly, based on its homology to the Restin protein, the rat 1p protein may be associated with the cytoskeleton and may modulate the activity of potassium channels, e.g., Kv4, via its association to the cytoskeleton.

25

EXAMPLE 19: IDENTIFICATION AND CHARACTERIZATION OF RAT 7s

In this example, the identification and characterization of the gene encoding rat 7s is described. Partial rat 7s was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Rat 7s is the rat ortholog of the human vacuolar H(+)-ATPase catalytic subunit A (Accession Number P38606 and B46091) described in, for example, van Hille B. *et al.* (1993) *J. Biol. Chem.* 268 (10), 7075-7080.

30 The nucleotide sequence of the partial length rat 7s cDNA and the predicted amino acid sequence of the rat 7s polypeptide are shown in Figure 29 and in SEQ ID NOs:58 and 59, respectively. The rat 7s cDNA encodes a protein having a molecular weight of approximately 28.6 kD and which is 270 amino acid residues in length.

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Rat 7s binds rKv4.3N and rKv4.2N with preference for rKv4.3N in yeast two-hybrid assays. In contrast, 7s does not bind rKv1.1N, indicating that the 7s-Kv4N interaction is specific.

- 5 Rat 7s is expressed at significantly higher levels in the brain and the kidney than
in the lung, liver, heart, testes, and skeletal muscle, as determined by northern blot
analysis.

**EXAMPLE 20: IDENTIFICATION AND CHARACTERIZATION OF
RAT 29x AND 25r**

10 In this example, the identification and characterization of the gene encoding rat
29x is described. Rat 29x was isolated as a positive clone from the yeast two-hybrid
screen described above, using rKv4.3N as a bait. Rat 25r is a splice variant of 29x.
They differ in the 5' untranslated region, but are identical in the coding region and at the
amino acid level.

15 The nucleotide sequence of the rat 29x cDNA and the predicted amino acid
sequence of the rat 29x polypeptide are shown in Figure 30 and in SEQ ID NOS:60 and
61, respectively. The rat 29x cDNA encodes a protein having a molecular weight of
approximately 40.4 kD and which is 351 amino acid residues in length.

The nucleotide sequence of the rat 25r cDNA is shown in Figure 31 and in SEQ
20 ID NO:62. The rat 25r cDNA encodes a protein having a molecular weight of
approximately 40.4 kD and which is 351 amino acid residues in length.

Rat 29x is expressed in the spleen, lung, kidney, heart, brain, testes, skeletal
muscle and liver, with the highest level of expression being in the spleen and the lowest
being in the liver.

25 Rat 29x binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast
two-hybrid assays. In contrast, 29x does not bind rKv1.1N, indicating that the 29x-
Kv4N interaction is specific.

Rat 29x is identical at the amino acid level to rat SOCS-1 (Suppressor Of
Cytokine Signaling) described in Starr R. *et al.* (1997) *Nature* 387: 917-921; to JAB
30 described in Endo T.A. *et al.* (1997) *Nature* 387: 921-924; and to SSI-1 (STAT-induced
STAT inhibitor-1) described in Naka T. *et al.* (1997) *Nature* 387:924-928. These

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proteins are characterized in that they have an SH2 domain, bind to and inhibit JAK kinase, and, as a result, regulate cytokine signaling.

As used herein, the term "SH2 domain", also referred to a Src Homology 2 domain, includes a protein domain of about 100 amino acids in length which is involved in binding of phosphotyrosine residues, *e.g.*, phosphotyrosine residues in other proteins. The target site is called an SH2-binding site. The SH2 domain has a conserved 3D structure consisting of two alpha helices and six to seven beta-strands. The core of the SH2 domain is formed by a continuous beta-meander composed of two connected beta-sheets (Kuriyan J. *et al.* (1997) *Curr. Opin. Struct. Biol.* 3:828-837). SH2 domains function as regulatory modules of intracellular signaling cascades by interacting with high affinity to phosphotyrosine-containing target peptides in a sequence-specific and strictly phosphorylation-dependent manner (Pawson T. (1995) *Nature* 373:573-580). Some proteins contain multiple SH2 domains, which increases their affinity for binding to phosphoproteins or confers the ability to bind to different phosphoproteins. Rat 29x contains an SH2 domain at amino acid residues 219-308 of SEQ ID NO:61.

Tyrosine phosphorylation regulates potassium channel activity (Prevarska N.B. *et al.* (1995) *J. Biol. Chem.* 270:24292-24299). JAK kinase phosphorylates proteins at tyrosines and is implicated in the regulation of channel activity (Prevarska N.B. *et al. supra*). Accordingly, based on its homology to SOCS-1, JAB, and SSI-1, rat 29x may modulate the activity of potassium channels, *e.g.*, Kv4, by modulating JAK kinase activity.

**EXAMPLE 21: IDENTIFICATION AND CHARACTERIZATION OF
RAT 5p**

In this example, the identification and characterization of the gene encoding rat 5p is described. Rat 5p was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait.

The nucleotide sequence of the rat 5pc DNA and the predicted amino acid sequence of the rat 5p polypeptide are shown in Figure 32 and in SEQ ID NOs:63 and 64, respectively. The rat 5p cDNA encodes a protein having a molecular weight of approximately 11.1 kD and which is 95 amino acid residues in length.

5 Rat 5p binds rKv4.3N and rKv4.2N with similar strength in yeast two-hybrid assays. In contrast, 5p does not bind rKv1.1N, indicating that the 5p-Kv4N interaction is specific.

Rat 5p is expressed in the spleen, lung, skeletal muscle, heart, kidney, brain, liver, and testes, as determined by northern blot analysis.

10 The rat 5p is identical to rat Calpastatin I light chain or P10 (Accession Number P05943). P10 binds and induces the dimerization of annexin II (p36). P10 may function as a regulator of protein phosphorylation in that the p36 monomer is the preferred target of a tyrosine-specific kinase (Masiakowski P. *et al.* (1998) *Proc. Natl. Acad. Sci. U.S.A.* 85 (4): 1277-1281).

15 Tyrosine phosphorylation regulates the activity of potassium channels (Prevarskaya N.B. *et al. supra*). Thus, due to its identity to P10, rat 5p may modulate the activity of potassium channels, e.g., Kv4, by modulating the activity of a tyrosine-specific kinase.

20 **EXAMPLE 22: IDENTIFICATION AND CHARACTERIZATION OF
RAT 7q**

In this example, the identification and characterization of the gene encoding rat 7q is described. Rat 7q was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Full length rat 7q was obtained by RACE 25 PCR.

The nucleotide sequence of the rat 7q cDNA and the predicted amino acid sequence of the rat 7q polypeptide are shown in Figure 33 and in SEQ ID NOs:65 and 66, respectively. The rat 7q cDNA encodes a protein having a molecular weight of approximately 23.5 kD and which is 212 amino acid residues in length.

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Rat 7q binds rKv4.3N and rKv4.2N with same strength in yeast two-hybrid assays. In contrast, 7q does not bind rKv1.1N, indicating that the 7q-Kv4N interaction is specific.

Rat 7q is expressed in the heart, brain, spleen, lung, liver, skeletal muscle,
5 kidney, and testes, as determined by northern blot analysis.

Rat 7q is identical to RAB2 (rat RAS-related protein, Accession Number P05712) at the amino acid level. RAB2 appears to be involved in vesicular traffic and protein transport (Touchot N. *et al.* (1987) *Proc. Natl. Acad. Sci. U.S.A.* 84 (23): 8210-8214). Accordingly, based on its homology to RAB2, rat 7q may be involved in
10 potassium channel, e.g., Kv4, trafficking.

**EXAMPLE 23: IDENTIFICATION AND CHARACTERIZATION OF
RAT 19r**

In this example, the identification and characterization of the gene encoding rat
15 19r is described. Partial rat 19r was isolated as a positive clone from the yeast two-hybrid screen described above, using rKv4.3N as a bait. Full length rat 19r was obtained by RACE PCR.

The nucleotide sequence of the rat 19r cDNA and the predicted amino acid sequence of the rat 19r polypeptide are shown in Figure 34 and in SEQ ID NOS:67 and
20 68, respectively. The rat 19r cDNA encodes a protein having a molecular weight of approximately 31.9 kD and which is 271 amino acid residues in length.

Rat 19r is expressed in the heart, brain, spleen, lung, liver, skeletal muscle, kidney, and testes, as determined by northern blot analysis.

Rat 19r binds rKv4.3N and rKv4.2N with slight preference for rKv4.3N in yeast
25 two-hybrid assays. In contrast, 19r does not bind rKv1.1N, indicating that the 19r-Kv4N interaction is specific.

Rat 19r is identical to Rat phosphatidylinositol (PTDINS) transfer protein alpha (PTDINSTP, Accession Number M25758 or P16446) described in Dickeson S.K. *et al.* (1989) *J. Biol. Chem.* 264:16557-16564. PTDINSTP is believed to be involved in
30 phospholipase C-beta (PLC-beta) signaling, phosphatidylinositol transfer protein (PtdIns-TP) synthesis, secretory vesicle formation, and enhancement of

phosphatidylinositol 3-kinase (PtdIns 3-kinase) activity (Cunningham E. *et al.* (1995) *Curr. Biol.* 5 (7): 775-783; (1995) *Nature* 377 (6549): 544-547; and Panaretou C. *et al.* (1997) *J. Biol. Chem.* 272 (4): 2477-2485).

Accordingly, based on its homology with PTDINSTP, rat 19r may modulate 5 potassium channel, *e.g.*, Kv4, activity via the PLC-beta signaling pathway and/or the PtdIns 3-kinase signaling pathway. Rat p19r may also be involved in potassium channel, *e.g.*, Kv4, trafficking.

EXAMPLE 24: CHROMOSOMAL LOCALIZATION OF HUMAN 9q

10 In this example, the human PCIP 9q was chromosomally mapped using a radiation hybrid panel (Panel GB4). h9q mapped to a region of chromosome 10q that had been previously shown to contain a linkage with partial epilepsy, namely D10S192: 10q22-q24 (Ottman *et al.* (1995) *Nature Genetics* 10:56-60) (see Figure 43). Based on this observation, the present invention clearly demonstrates that the 9q family of 15 proteins can serve as targets for developing anti-epilepsy drugs and as targets for medical intervention of epilepsy.

Furthermore, h9q mapped to a region of chromosome 10q that had been previously shown to contain a linkage with IOSCA, namely D10S192 and D10S1265: 20 10q24- Nikali (Genomics 39:185-191 (1997)) (see Figures 42 and 43). Based on this observation, the present invention clearly demonstrates that the 9q family of proteins can serve as targets for developing anti-spinocerebellar ataxia drugs and as targets for medical intervention of spinocerebellar ataxia.

**EXAMPLE 25: KINETIC MODULATION OF KV4-CURRENT BY
25 ARACHIDONIC ACID IS DEPENDENT ON
K-CHANNEL INTERACTING PROTEINS**

The voltage-gated fast-inactivating Kv4 potassium channels are thought to underlie the dendritic A-current in central neurons and the transient outward current (I_{to}) in cardiac myocytes activating at subthreshold membrane potentials. It has been 30 reported that arachidonic acid (AA) inhibits both the current formed by Kv4 alpha

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subunits in heterologous cells and the A-current from macropatches excised from hippocampal neurons. However, actions of AA differ in that the neuronal inhibition was associated with kinetic changes that were absent *in vitro*. Most strikingly, the rate of inactivation was considerably increased upon AA application.

- 5 As indicated above, current formed by the Kv4/KChIP combination *in vitro* resembles in many aspects the A-current or I_o recorded *in vivo*. In this Example, the role of KChIPs in the kinetic modulation of Kv4-current by arachidonic acid is investigated using art known techniques (described in, for example, An *et al.* (2000) *Nature* 403:553-6; Keros, S. and McBain, C. J. (1997) *J. Neuroscience* 17: 3476-87; and
10 Villarroel, A. and Schwarz, T. L. (1996) *J. Neuroscience* 16:2522-32). In Oocytes and in CHO cells, AA inhibited peak amplitude of Kv4 independent of KChIP1. In contrast, perfusion of 10 mM of AA resulted in faster inactivation of Kv4 co-expressed with KChIP1, but did not change the rate of inactivation of Kv4 expressed alone. Thus, the AA effect on inactivation of Kv4/KChIP1 *in vitro* mimics that of the A-current in
15 excised neuronal patches. Taken together with the results reported above, these data support the notion that KChIPs are Kv4 auxiliary subunits and that kinetic modulation of Kv4 by AA is dependent on the presence of KChIPs.

20 **EXAMPLE 26: K-CHANNEL INTERACTING PROTEIN-2 (KChIP2)
SPLICE VARIANTS, CHROMOSOMAL ORGANIZATION
AND LOCALIZATION**

In the present Example, variants of KChIP2 and their chromosomal organization were identified using standard techniques. KChIP2 genes are highly conserved at the
25 amino acid level among human, rat, and mouse. Multiple human splice variants were identified by database mining and cDNA library screening. Alternative splicing gives rise to N-terminal domains that are variable in length, but the core C-terminal domain is sufficient for associating with and modulating Kv4. The human KChIP2 gene spans approximately 18 kb in the q23 region of human chromosome 10 between WI-8488 and
30 WI-6750. This region is syntenic to mouse chromosome 19 between D19Mit40 and D19Mit11. A rat variant discovered by database mining changed the last five amino acids and maintained its ability to associate with and modulate Kv4. Therefore, these multiple variants of KChIP2 appear to function similarly in Kv4 modulation.

Equivalents

- Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention
- 5 described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. An isolated nucleic acid molecule selected from the group consisting of:
- 5 a) a nucleic acid molecule comprising a nucleotide sequence which
is at least 60% identical to the nucleotide sequence of SEQ ID NO:1, SEQ ID
NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID
NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ
ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31,
10 SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID
NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ
ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the DNA insert of the plasmid
deposited with ATCC as Accession Number 98936, 98937, 98938, 98939,
98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949,
15 98950, 98951, 98991, 98993, 98994, or PTA-316, or a complement thereof;
- 20 b) a nucleic acid molecule comprising a fragment of at least 583
nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID
NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID
NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ
ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29,
25 SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID
NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ
ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, the DNA insert
of the plasmid deposited with ATCC as Accession Number 98936, 98937,
98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947,
98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, or a
complement thereof;
- 30 c) a nucleic acid molecule which encodes a polypeptide comprising
an amino acid sequence at least about 60% identical to the amino acid sequence
of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10,
SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID

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NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ
ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38,
SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID
NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or
5 an amino acid sequence encoded by the DNA insert of the plasmid deposited
with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941,
98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951,
98991, 98993, 98994, or PTA-316;

10 d) a nucleic acid molecule which encodes a fragment of a
polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID
NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID
NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ
ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32,
SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID
15 NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ
ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence
encoded by the DNA insert of the plasmid deposited with ATCC as Accession
Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944,
98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or
PTA-316, wherein the fragment comprises at least 15 contiguous amino acid
20 residues of the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID
NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID
NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ
ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34,
25 SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID
NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ
ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA
insert of the plasmid deposited with ATCC as Accession Number 98936, 98937,
98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947,
30 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316; and

e) a nucleic acid molecule which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule comprising SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, under stringent conditions.

2. The isolated nucleic acid molecule of claim 1 which is selected from the group consisting of:

a) a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, or a complement thereof; and

b) a nucleic acid molecule which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

25
3. The nucleic acid molecule of claim 1 further comprising vector nucleic acid sequences.

30
4. The nucleic acid molecule of claim 1 further comprising nucleic acid sequences encoding a heterologous polypeptide.

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5. A host cell which contains the nucleic acid molecule of claim 1.
6. The host cell of claim 5 which is a mammalian host cell.
- 5 7. A non-human mammalian host cell containing the nucleic acid molecule
of claim 1.
8. An isolated polypeptide selected from the group consisting of:
- 10 a) a fragment of a polypeptide comprising the amino acid sequence
of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10,
SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID
NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ
ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38,
15 SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID
NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or
an amino acid sequence encoded by the DNA insert of the plasmid deposited
with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941,
98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951,
20 98991, 98993, 98994, or PTA-316, wherein the fragment comprises at least 15
contiguous amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID
NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID
NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ
ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36,
25 SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID
NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or
SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the
plasmid deposited with ATCC as Accession Number 98936, 98937, 98938,
98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948,
30 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316;

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- 5 b) a naturally occurring allelic variant of a polypeptide comprising
the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ
ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ
ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26,
10 SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID
NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ
ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or
SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the
plasmid deposited with ATCC as Accession Number 98936, 98937, 98938,
15 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948,
SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID
NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ
ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35,
20 SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID
NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or
SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as
Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943,
25 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993,
98994, or PTA-316 under stringent conditions; and
30 c) a polypeptide which is encoded by a nucleic acid molecule
comprising a nucleotide sequence which is at least 60% identical to a nucleic
acid comprising the nucleotide sequence of SEQ ID NO:1, SEQ ID NO:3 SEQ
ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ
ID NO:15, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23,
SEQ ID NO:25, SEQ ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID
NO:33, SEQ ID NO:35, SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ
ID NO:50, SEQ ID NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58,
SEQ ID NO:69, or SEQ ID NO:71, or the DNA insert of the plasmid deposited

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with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

5 d) a polypeptide comprising an amino acid sequence which is at least 60% identical to the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

15 9. The isolated polypeptide of claim 8 comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316.

20 10. The polypeptide of claim 8 further comprising heterologous amino acid sequences.

25 30 11. An antibody which selectively binds to a polypeptide of claim 8.

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12. A method for producing a polypeptide selected from the group consisting of:

- a) a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316;
- b) a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the fragment comprises at least 15 contiguous amino acids of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26, SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the

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plasmid deposited with ATCC as Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993, 98994, or PTA-316; and

- 5 c) a naturally occurring allelic variant of a polypeptide comprising
the amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ
ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, SEQ
ID NO:18, SEQ ID NO:20, SEQ ID NO:22, SEQ ID NO:24, SEQ ID NO:26,
SEQ ID NO:28, SEQ ID NO:30, SEQ ID NO:32, SEQ ID NO:34, SEQ ID
NO:36, SEQ ID NO:38, SEQ ID NO:40, SEQ ID NO:49, SEQ ID NO:51, SEQ
10 ID NO:53, SEQ ID NO:55, SEQ ID NO:57, SEQ ID NO:59, SEQ ID NO:70, or
SEQ ID NO:72 or an amino acid sequence encoded by the DNA insert of the
plasmid deposited with ATCC as Accession Number 98936, 98937, 98938,
98939, 98940, 98941, 98942, 98943, 98944, 98945, 98946, 98947, 98948,
98949, 98950, 98951, 98991, 98993, 98994, or PTA-316, wherein the
15 polypeptide is encoded by a nucleic acid molecule which hybridizes to a nucleic
acid molecule comprising SEQ ID NO:1, SEQ ID NO:3 SEQ ID NO:5, SEQ ID
NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID
NO:17, SEQ ID NO:19, SEQ ID NO:21, SEQ ID NO:23, SEQ ID NO:25, SEQ
ID NO:27, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:33, SEQ ID NO:35,
20 SEQ ID NO:37, SEQ ID NO:39, SEQ ID NO:48, SEQ ID NO:50, SEQ ID
NO:52, SEQ ID NO:54, SEQ ID NO:56, SEQ ID NO:58, SEQ ID NO:69, or
SEQ ID NO:71, or the DNA insert of the plasmid deposited with ATCC as
Accession Number 98936, 98937, 98938, 98939, 98940, 98941, 98942, 98943,
98944, 98945, 98946, 98947, 98948, 98949, 98950, 98951, 98991, 98993,
25 98994, or PTA-316 under stringent conditions;

comprising culturing the host cell of claim 5 under conditions in which the
nucleic acid molecule is expressed.

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13. A method for detecting the presence of a polypeptide of claim 8 in a sample comprising:

- a) contacting the sample with a compound which selectively binds to the polypeptide; and
- 5 b) determining whether the compound binds to the polypeptide in the sample to thereby detect the presence of a polypeptide of claim 8 in the sample.

14. The method of claim 13, wherein the compound which binds to the 10 polypeptide is an antibody.

15. A kit comprising a compound which selectively binds to a polypeptide of claim 8 and instructions for use.

16. A method for detecting the presence of a nucleic acid molecule in claim 1 in a sample comprising:

- a) contacting the sample with a nucleic acid probe or primer which selectively hybridizes to the nucleic acid molecule; and
- 20 b) determining whether the nucleic acid probe or primer binds to a nucleic acid molecule in the sample to thereby detect the presence of a nucleic acid molecule of claim 1 in the sample.

17. The method of claim 16, wherein the sample comprises mRNA molecules and is contacted with a nucleic acid probe.

25

18. A kit comprising a compound which selectively hybridizes to a nucleic acid molecule of claim 1 and instructions for use.

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19. A method for identifying a compound which binds to a polypeptide of claim 8 comprising:

- a) contacting the polypeptide, or a cell expressing the polypeptide with a test compound; and
- 5 b) determining whether the polypeptide binds to the test compound.

20. The method of claim 19, wherein the binding of the test compound to the polypeptide is detected by a method selected from the group consisting of:

- 10 a) detection of binding by direct detection of test compound/polypeptide binding;
- b) detection of binding using a competition binding assay; and
- c) detection of binding using an assay for PCIP activity.

21. A method for modulating the activity of a polypeptide of claim 8 comprising contacting the polypeptide or a cell expressing the polypeptide with a compound which binds to the polypeptide in a sufficient concentration to modulate the activity of the polypeptide.

22. A method for identifying a compound which modulates the activity of a polypeptide of claim 8 comprising:

- 20 a) contacting a polypeptide of claim 8 with a test compound; and
- b) determining the effect of the test compound on the activity of the polypeptide to thereby identify a compound which modulates the activity of the polypeptide.

25
23. A method for identifying a compound capable of treating a disorder characterized by aberrant PCIP nucleic acid expression or PCIP protein activity comprising assaying the ability of the compound or agent to modulate the expression of the PCIP nucleic acid molecule of claim 1 or the activity of the PCIP polypeptide of 30 claim 8, thereby identifying a compound capable of treating a disorder characterized by aberrant PCIP nucleic acid expression or PCIP protein activity.

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24. The method of claim 23, wherein the disorder is a CNS disorder.
- 5 25. The method of claim 24, wherein the disorder is epilepsy.
- 10 27. The method of claim 24, wherein the disorder is spinocerebellar ataxia.
28. The method of claim 23, wherein the disorder is a cardiovascular disorder.
- 15 29. The method of claim 28, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.
30. A method for determining if a subject is at risk for a disorder characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity comprising detecting, in a sample of cells from the subject, the presence or absence of a genetic lesion, wherein the genetic lesion is characterized by an alteration affecting the integrity of a gene encoding the PCIP polypeptide of claim 8 or misexpression of the PCIP nucleic acid molecule of claim 1.
- 20 31. The method of claim 30, wherein the disorder is a CNS disorder.
32. The method of claim 31, wherein the disorder is epilepsy.
- 25 33. The method of claim 31, wherein the disorder is spinocerebellar ataxia.
34. The method of claim 30, wherein the disorder is a cardiovascular disorder.
- 30 35. The method of claim 34, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

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36. A method for identifying a subject suffering from a disorder characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity comprising obtaining a biological sample from the subject, and detecting in the 5 sample, the presence or absence of a genetic lesion, wherein the genetic lesion is characterized by an alteration affecting the integrity of a gene encoding the PCIP polypeptide of claim 8 or misexpression of the PCIP nucleic acid molecule of claim 1, thereby identifying a subject suffering from a disorder characterized by aberrant or abnormal PCIP nucleic acid expression and/or PCIP protein activity.

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37. The method of claim 36, wherein the disorder is a CNS disorder.

38. The method of claim 37, wherein the disorder is epilepsy.

15

39. The method of claim 37, wherein the disorder is spinocerebellar ataxia.

40. The method of claim 36, wherein the disorder is a cardiovascular disorder.

20

41. The method of claim 40, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.

42. A method for treating a subject having a potassium channel associated disorder comprising administering to the subject a PCIP polypeptide of claim 8 or 25 portion thereof such that treatment occurs.

43. The method of claim 42, wherein the disorder is a CNS disorder.

44. The method of claim 43, wherein the disorder is epilepsy.

30

45. The method of claim 43, wherein the disorder is spinocerebellar ataxia.

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46. The method of claim 42, wherein the disorder is a cardiovascular disorder.
- 5 47. The method of claim 46, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.
- 10 48. A method for treating a subject having a potassium channel associated disorder comprising administering to the subject a nucleic acid encoding a PCIP polypeptide of claim 8 or portion thereof such that treatment occurs.
- 15 49. The method of claim 48, wherein the disorder is a CNS disorder.
50. The method of claim 49, wherein the disorder is epilepsy.
- 15 51. The method of claim 49, wherein the disorder is spinocerebellar ataxia.
52. The method of claim 48, wherein the disorder is a cardiovascular disorder.
- 20 53. The method of claim 52, wherein the cardiovascular disorder is associated with an abnormal I_{to} current.
- 25 54. Use of the compound identified in the method of claim 23 to treat a potassium channel associated disorder.

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POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR

Abstract of the Disclosure

- The invention provides isolated nucleic acids molecules, designated PCIP
- 5 nucleic acid molecules, which encode proteins that bind potassium channels and modulate potassium channel mediated activities. The invention also provides antisense nucleic acid molecules, recombinant expression vectors containing PCIP nucleic acid molecules, host cells into which the expression vectors have been introduced, and nonhuman transgenic animals in which a PCIP gene has been introduced or disrupted.
- 10 The invention still further provides isolated PCIP proteins, fusion proteins, antigenic peptides and anti-PCIP antibodies. Diagnostic methods utilizing compositions of the invention are also provided.

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886 > 35 Cu m 63 93 > 60.6

HUMAN IV DNA (CD:225-87)

MANUFACTURING PROCESS

IMGGAGMTGFTSSLQTQKQRPSKDIEDELEMNTVCHRPEGLQEATQNTPKRELQVLYRGFKNECPSGVVNEDTFKQIYAQ
FFFPHGDASTAYHLENAFDITDITQTSVFKEDFTALTSILLRGTVHEKLRTWTFNLYDINKDGYINKEEMMDIVKAIXDMMGK
YTYPVPLKEDTPRHOYDVFFORMDKURKGDIYTLDLDEFLESCOEDDNIRMSLOFFONVM

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RAT 1vN (r1vN) DNA (CD: 339-1037)

GGCACACAACCCCTGGATTCTCGGAGAATATGCCGTGAGGTGTTGCCAATTATTAGTTCTCTGGCTAGCAGATGTTA
GGGACTGGTaaGCCTTGAGAAATTACCTTAGGAAAACGGGAAATAAAGCAAAGATTACCATGAATTGCAAGATTA
CCTAGCAATTGCAAGGTtagGAGGAGAGGGTGGAGGGCGGAGTAGACAGGGAGGGAGGAAAGtgaGAGGAAGCTAGGC
TGGTGGAAATAACCCCTGCACTTGGAACAGCGGCAAAGAACGGGATTTCCAGCTTaaATGCCIGCCCGCTCTGGCTT
GCCCTACCGGGAACGGAGATGGTGAACCCAGGGCAGTCTGAAGGGCTCAGACCTGGGGATAGTAGTGGCTGTGTT
CTCTCTGAAACTACTGCACTACCTCGGCTGATTGACTTGTGGATGACAAGATCGAGGATGATCTGGAGATGACCATGG
TTTGCCATCGGCCAGGGACTGGGAGCTGGAGCAGCTTGAGGACAGACAGAACTTACCAAGAGAGAACTGCAAGTCCTTACCG
GGATTCAAAAACGAGTCCCCAGTGGTGTGTTAACGAAGAGACATTCAAGCAGATCTACGCTCAGTTTCCCTCATGG
AGATGCCAGCACATACGCACATTACCTCTTCAATGCCCTGCACACCACCCAGACAGGGCTGTAAAGTCAGGACTTTG
TGACTGCTCTGCGATTTACTGAGAGGAACGGTCCATGAAAAACTGAGGTGGACGTTAATTTGACATCAATAAA
GACGGCTACATAAAACAAAGAGGAGATGATGGACATAGTGAAGGCCATCTATGACATGATGGGGAAATAACACCTATCCTGT
GCTCAAAGGGACACTCCCAGGCAGCACGTCAGCTTCTTCAGAAAATGGATAAAAATAAGATGGCATTGTAACGT
TAGACGAATTCTCGAGTCAGTCAGGAGGATGACAACATCATGAGGTCTCTACAGCTGTTCAAATGTCATGTAACGT
AGGACACTGGCCATCTGCTCTCAGAGACACTGACAACACCTCAATGCCCTGATCTGCCCTGTCAGTTTACACAT
CAACTCTGGGACAGAAAATCCTTTACACTTGGAGAATTCTCTGCTGAAGACTTCTACAAAACCTGGCACCGAGTG
GCTCAGTCTCTGATGCCAACTCTCCCTCCCTCCCTGAGGGACGAGCTGAATCCGAAGTTGTTGGAAAGC
ATGCCCATCTCCATGCTGCTGCTGCCCTGTTGAGCTTAAACAGTAGTCACAGCTGTTCTGCG
TATACAGATCCCCACTCACTGCTCTAAGTCAGGCAGACCCCTGATCAATCTGAACCAAATGTCACCCATCTGGATGG
CCTCCCAAGCCAATGCGCTGCTCTCTCCCTGTTGGAGAAAAGAACGCTCTACAGACCACTTAGAGCTTACCATGA
AAATACTGGGAGGGCAGCACSTAACACATGTAGAATAGGACTGAATTATTAAGCATGGGGATCAGATGATGCAAACA
GCCCATGTCATTTTTTCCAGAGGTAGGGACTAATAATTCTCCACACTAGCACCTACGATCATAGAACAGTCTTT
AACACATCCAGGAGGGAAACCGCTGCCAGTGGCTATCCCTCTCCATCCCTGCTCAAGCCAGCACTGCACTG
CTCCCGGAAGGTCAGARTGCTGTGAAATGCTGAACCTTATACCTGTTATAATCAAAACAGAACTATTCGTCAC
AAAAAAAAAAAAAAA

Fig. 2

RAT 1vN (r1vN) PROTEIN

MLTQGESEGLQTLGIVVVLCSSLKLLHYLGLIDLSDDKIEDDLEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEC
PSGVVNEETFKQIYAQFFPHGDASTYAHYLNFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLRWTFNLYDINKDGYINK
EEMMDIVKAIYDMMGKYTYPVLKEDTPRQHVDFFFQKMDKNKDGIVTLDLFESQEDDNIMRSILQLFQNVM

Fig. 2 Continued

MOUSE 1V (CD:477-1127)

CGGGCCCCCTGAGATCCAGCCGAGCGGGGGCGAGCGGCCGGTGGCAGCAGGGCGGGCGGGCGAGCGCAGCTCCCG
 CACCGCACGCAGCGCGCCGCTCGGCAGCCTCGGCCGTGGCGACGCCGGCCCGTGTCAAACATCAGGCAGGCTTGGGG
 CTCTGGGCTCGGGCCTCGGAGAACCGAGTGGCCCGTGGGTGCCCGCACCGGGGGCGCCGTGCAAGGCTCCCGCAGC
 CTCTGGCCCTGGGAGTCAGTCATGTGCTGGCTGAAGAACGGCAGGCCACGAGCTCCAGGCAGGCCCGCCACAGTTT
 TCTGAATAACCAAGCTGAGCGAGCTCTCGGGCTTTTGCTCTCCTCTCTCTCCAAATTCAAAGTGGCA
 ATCCACACCGATTTCTTTCAGGGGAGGGAGAGACAGGGCTGGGTCCAAGACGCACACAAGTCTCGTGCCATGG
 GGGCCGTCATGGGACTTCTCCCTCGACAGACAAACAAAGCGACCCCTAAAGACAAGATTGAGGATGAGCTAGAG
 ATGACCATGGTTGCCACGGCCCTGAGGGACTGGAGCAGCTTGAGGGCACAGACAAACTTCAACCAAGAGAGAACTGCAAGT
 CTTGTACCGGGGATTCAAAAACAGAGTGCCTAGCGGTGTTCAATGAAGAAAATTCAGCAGATCTACGCTCAGTTT
 TCCCTCACGGAGATGCCAGCACATATGCACATATTACCTCTTCAATGCCCTCGACACCACCCAGACAGGCTCTGTAAGTTC
 GAGGACTTGTGACTGCTCTGATTTACTGAGAGGGACAGTCCATGAAAACATAAGGTGGACGTTAATTGTATGA
 CATCAATAAAAGACGCCATACAAAAAGAGGAGATGATGGACATAGTCAGGCATCTGATGACATGATGGGAAATACA
 CCTATCCTGTGCTCAAAGAGGACACTCCAGGCAGCATGTGGATGCTCTCCAGAAAATGGATAAAAATAAGATGGC
 ATTGTAACGTTAGATGAATTCTGAAATCATGTCAGGAGGATGACAACATCATGAGATCTCATGCTGTTCAAATGT
 CATGTAACGTGAGGACACTGCCATTCTGCTCTGAGACACTGACAAACACCTTAATGCCCTGATGCCCTGTTCAA
 TTTTACACACCAACTCTGGGACAGAAAATACCTTTACCTTGGAGAATTCTCTGCTGAAGACTTCTACAAAACCTG
 GCACCCAGCTGGCTCTGCTCTGAGGGAGCAGGGAGATCCGACTTGTGTTGGAGCATGCCATCTCATGCTGCTG
 CCCTGTGAAAGGCCCTCTGCTGAGCTTAATCAATAGTCACAGTTTATGCTTACACATATCCCACACTCCTC
 CAAGTCAGGCAGACTCTGATGAATCTGAGCCAAATGTCACCCATCTCCGATGCCCTCCAAGCCAATGTGCTGCTCT
 CTTCTCTGGTGGGAGAAAAGAGTGTCTACGGAACAATTAGAGCTTACCATGAAAATATTGGGAGAGGAGCAGCACCTAAC
 ACATGTGAAATAGGACTGAAATTATTAACCATGGTGAATATCAGATGATGTCAAATTGCCCATGTCATTGTTCAAAGTAG
 GGACAANTGATTCTCCCACACTAGCACCCTGTTGATAGAGCAAGTCTCTAACATGCCAGAAGGGAAACACTGTC
 GTGGTCTATCCCTCTCCATCCCTGCTCAAACCCAGCAGTCATGTCCTCCAAGAAGGTCCAGAATGCTCGA
 CGCTGTACTTTATACCCCTGTTCTAAATCAAACAGAACTATTGTTGAAAAAAAAAAAAAA

MOUSE 1V PROTEIN

MGAVMGTFSSLQTKQRPSDKIEDELEMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPGVVNEETFKQIYAQ
 FFPFHGDASTYAHYLFNAFDTTGTGSVKFEDFTVTLALSILLRTVHEKLRLRTFWNLIDINKDGYINKEEMMDIVKA
 VTYPVLKEDTPRQHVDFVFFQKMDKNDGIVTLDEFLESCQEDDNIMRSLQLFQNVM

Fig. 3

RAT 1VL DNA (CD:31-714)

GTCCCCAAGTCGACACAAGTCTTCGCTGCCATGGGGCCGTATGGGTACCTCTCGTCCCTGCAGACCAAAACAAAGCG
 ACCCTCTAAAGACATCGCCTGGTGGTATTACAGTATCAGAGAGACAAGATCGAGGATGATCTGGAGATGACCATGGTT
 GCCATCGGCCTGAGGGACTGGAGCAGCTTGAGGCACAGACGAACCTCACCAAGAGAGAACTGCAAGTCCTTACCGGG
 TTCAAAACAGAGTCCCCAGTGGTGTGGTTAACAGAGACATTCAGCAGATCTACGCTCAGTTTCCCTCATGGAGA
 TGCGAGCACATACGCACATTACCTCTCAATGCCTTCGACACCACCCAGACAGGCTCTGTAAGTTCGAGGACTTGTGA
 CTGCTCTGCGATTTACTGAGAGGAACGGTCCATGAAAAACTGAGGTGGACGTTAATTGTACGACATCAATAAACAC
 GGCTACATAACAAAGAGGAGATGATGGACATAGTGAAAGCCATCTATGACATGATGGGAAATACACCTATCCTGTGCT
 CAAAGAGGACACTCCAGCAGCACGTGGAGCTTCTCCAGAAAATGGATAAAATAAGATGCCATTGTAACCTTAG
 ACGAATTCTCGAGTCCTGTCAGGAGGATGACAACATCATGAGGTCTCTACAGCTGTCCTTACAGCTGTTCAAATGTCATGTAACGTAG
 ACACTGGGCATCCTGCTCTCAGACACACTGACAACACCTCAATGCCCTGATCTGCCCTGTTGCTTACACATCAA
 CTCTGGGAACAGAAATACCTTTACCTTGGAGAATTCTCTGCTGAAGACTTCTACAAAACCTGGCACCCGTGGT
 CAGTCTCTGATTGCCAACTCTCCTCCCTCCTCTCTGAGAGGGACGAGCTGAAATCCGAAGTTGTTTGGAAAGCATG
 CCCATCTCCATGCTGCTGCCCTGTGGAAGGCCCTCTGCTGAGCTTAAACAGTAGTGACAGTTTCTGCGTAT
 ACAGATCCCCAACTCACTGCCCTCAAGTCAGGCAGACCCGTATCAATCTGAACCAAATGTGCACCATCCTCCGATGGCCT
 CCCAAGCCAATGTGCTGCTCTCTCCCTCTGGTGGAAAGAAAGAACGCTCTACAGGCACCTAGAGCTTACCATGAAAA
 TACTGGGAGGGCAGCACCACACATGTAGAATAGGACTGAATTATTAAGCATGGTGGTATCAGATGATGCAAACAGCC
 CATGTCATTTTTTCCAGAGGTAGGGACTAATAATTCTCCACACTAGCACCTACGATCATGAAACAATCTTAAACA
 CATCCAGGAGGGAAACCGCTGCCAGTGGTCTATCCCTCTCCATCCCTGCTCAAGCCCAGCAGTCATGTCATGTCCTCC
 CGGAAGGTCAGAATGCCCTGTGAAATGCTGTAACTTTATACCTGTTATAATCAATAAACAGAACTATTCGTACAAAA
 AAAAAAAAAAAAAA

RAT 1VL PROTEIN

MGAVMGTFSLLQTKQRPSKDIAWWYYQYQRDKIEDDLEMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPGVV
 NEETFKQIYAQFFPHGDASTYAHYLFNAFDTTQTGSVKFEDFTVTLSSILLRGTVHEKLWRWTFNLYDINKDGYINKEEMMD
 IVKAIYDMMGKYTYPVLKEDTPRQHVDFVFFQKMDKNKDGIVTLDDEFLESCQEDDNIMRSIQLFQNV

Fig. 4

MOUSE 1VL DNA (CD:77-760)

ATCCACACCGATTCTTTCAGGGGAGGGAAAGAGACAGGGCTGGGTCCAAGACGCACACAAGTCTCGCTGCCATGG
 GGGCGTCACTGGGACTTTCTCCTCCTGCAGACCAAACAAAGGCACCCCTAAAGACATCGCTGGTGTATTACAG
 TATCAGAGAGACAAGATTGAGGATGAGCTAGAGATGACCATTGTTGCCACCGGCTGAGGGACTGGAGCAGCTTGAGGC
 ACAGACGAACCTCACCAAGAGAGAACTGCAAGTCTGTACCGGGATTCAAAAACAGAGTGCCCCTAGCGGTGTGGTCAATG
 AAGAACATTCAAGCAGATCTACGCTCAGTTTCCCTCACGGAGATGCCAGCACATATGCACATTACCTCTTCAATGCC
 TTGACACACCAGCAGAGGCTCTGTAAGTCAGGACTTTGACTGCTCTGCAATTACTGAGAGGGACAGTCCA
 TGAAAACATAAGGTGGACGCTTAATTGTATGACATCAAAAGACGGCTACATAAAACAAAGAGGGAGATGGACATAG
 TCAAAGCCATCTATGACATGATGGGAAATACACCTATCCTGCTCAAAGAGGACACTCCAGGCAGCATGTGGATGTC
 TTCTTCCAGAAAATGGATAAAATAAAGATGGCATTGTAACGTTAGATGAAATTCTTGAATCATGTCAGAGGGATGACAA
 CATCATGAGATCTCTACAGCTGTTCAAATGTATGTAAGTGGACACTGGCATTCTGCTCTCAGAGACACTGACAA
 ACACCTTAATGCCCTGATGCCCTGTTCCAATTTCACACCAACTCTGGACAGAAAATACCTTTACACTTGGAA
 GAATTCTCTGCTGAAGACTTCTACAAAACCTGGACCAGTGGCTGCTCTGAGGGACGAGCGGAGATCCGACTTG
 TTTTGGAAAGCATGCCCATCTCTCATGCTGCGCTGTGGAAGGCCCTCTGCTTGAGCTTAATCAATGTCACAGTT
 TTATGCTTACACATATCCCCACTACTGCCCTCAAGTCAGGAGACTCTGATGAATCTGAGCCAAATGTGCACCATCT
 CCGATGGCCTCCAAAGCCAATGTGCGCTGCTCTCTCTCTGGTGGAAAGAAAGAGTGTCTACGGACAAATTAGAGCTT
 ACCATGAAAATATTGGAGAGGCAGCACCTAACACATGTAGAAATAGGACTGAAATTAAAGCATGGTGATATCAGATGAT
 GCAAATTGCCATGTCTTCTTCAAGGTAGGGACAAATGATTCTCCCAACTAGCACCTGTGGTCAAGAGCAAGTC
 TCTAACATGCCAGAAGGGAAACACTGTCAGTGGCTATCCCTCTCCATCCCTGCTCAAACCCAGCACTGCAT
 GTCCCTCCAAGAGGTCCAGAATGCCCTGCGAACAGCTGTACTTTATACCTGTTCAATCAAAACAGAACTATTCG
 TACAAAAAA

MOUSE 1VL PROTEIN

MGAVMGTSSLQTKQRPSKDIAWYYQYQRDKIEDELEMTMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNECPGVV
 NEETFKQIYAQFFPHGDASTYAHYLFNAFDTTGTGSVKFEDFVTALSILLRTVHEKLRWTFNLYDINKDGYINKEEMMD
 IVKAIYDMMGKYTYPVLKEDTPRQHVDFQMDKNKDGIIVTLDEFLESCQEDDNIMRSLQLFQNV

Fig. 5

RAT 1VN DNA (FIRST-PASS, PARTIAL; CD: 345-955)

GTCCGGGACACAACCCCTGGATTCTCGAGAATATGCCGTGACGGTGTGCCAATTATTAGTTCTTGGCTAGCAGA
 TGTTTAGGGACTGGTTAACGCCCTTGGAGAAATTACCTTACGGAAAACGGGGAAATAAAAGCAAAGATTACCATGAATTGCA
 AGATTACCTAGCAATTGCAAGGTAGGAGAGAGGTGGAGGGGGAGTAGACAGGGAGGGAGGAAGTGAAGAGGAAG
 CTAGGCTGGTGGAAATAACCCCTGCACCTGGAACAGCGCAAAAGAACGGCGATTTCAGCTTAATGCTGCCCGCGT
 CTGCTTGCTACCCGGAACGGAGATGTTGACCCAGGGCGAGCTGAAAGGGCTCCAGACCTTGGGATAGTAGTGGTCT
 GTGTTCCCTCTGAAACTACTGCACTACCTCGGCTGATTGACTTGTGCGGATGACAAGATCGAGGATGATCTGGAGATGA
 CCATGTTTCCATCGGCCATGGGACTGGAGCAGCTTGAGGCCACAGACGAACTTACCAAGAGAGAACTGCAAGTCCT
 TACCGGGGATTCAAAACGAGTGCCTGAGGGACTGGAGCAGCTTGAGGCCACAGACGAACTTACCAAGAGAGAACTGCAAGTCCT
 TCATGGAGATGCCAGCACATACGCACATTACCTCTTCATGCCCTTCAGACCACCCAGACAGGCTCTGTAAGGTTGAG
 ACTTTGTGACTGCTCTGCTGATTTACTGAGAGGAACGGTCCATGAAAAACTGAAAGTGGACGTTAATTGTACGACATC
 AATAAAGACGGCTACATAAAACAAAGAGGAGATGATGGACATAGTGAAGGCCATCTATGACATGATGGGAAATACACCTA
 TCTTGTGCTCAAAGAGGACACTTCCAGGCACCGTGGACGCTTCTCCAGAAAATGGATAAAAATAAGATGG

RAT 1VN PROTEIN (PARTIAL)

MLTQGESEGLQTLGIVVVLCSSLKLLHYLGLIDLSDDKIEDDLEMVCHRPEGLEQLEAQTNFTKRELQVLYRGFKNEC
 PSGVVNEETFKXIYAQFFPHGDASTYAHYLNFNAFDTTQTGSVKFEDFVTALSILLRGTVHEKLWTFNLYDINKGYINK
 EEMMDIVKAIYDMMGKYTYLVLKEDTSRQHVDVFFQKMDKNKD

Fig. 6

HUMAN 9Q1 DNA (CD:207-1019)

CTCACCTGCTGCCCTAGTGTCCCTCCTGCTCCAGGACCTCCGGTAGACCTCAGACCCCCGGGCCATTCCCAGACTCA
 GCCTCAGCCGGACTTCCCAGCCCCGACAGCACAGTAGGCCAGGGGGCGCCGTGTGAGCCCTATCCCGGCCACC
 CGCGCCCCCTCCACGCCCGGGCGGGAGCGGGCGCCGGGGCATCGGGGCCAGGGCGCAAGGAGAGTTGTCCG
 ATTCCCAGACCTGGACGGCTCTACGACAGCTACGGGCCACCTCCAGGGCCACTAAAAAGCCTGAACAGCGA
 TTCCCTCAAGCTGCTGCCGTCTCGGGGCCCAAGCCCTGCCTCAGTCAGTAAACATTAGCCGCCAGCCTCCCTCG
 CCCCCACAGACCCCGCTGCGACCCAGACACCGTGAGATGAATTGAAATTGTCACCCGTGTGTCACGGCCTGAGG
 GTCTGGAGCAGCTGCAGGACAAACCAAATTACGCGCAAGGAGTTGCAGGTCTGTACCGGGCTCAAGAACGAATGT
 CCCAGCGGAATTGTCATGAGGAGAACCTCAAGCAGATTACTCCAGTCTTCTCAAGGAGACTCCAGCACCTATGC
 CACTTTCTCTCAATGCCCTTGACACCAACCATGATGGTCGGTCAAGGAGACTTTGTGGCTGGTTGTGCGTGA
 TTCTTCGGGAACTGTAGATGACAGGCTTAATTGGGCTTCACCTGTATGACCTTAACAAGGACGGCTGCATCCAAG
 GAGGAATGCTGACATCATGAACTGCTCATCTATGACATGATGGCAAGTACAGTACCTGACTCCGGAGGGCCC
 AAGGGAACACGTGGAGGCTCTCCAGAAGATGGACAGAAACAAGGATGGTGTGGTACATTGAGGAATTCAATTGAGT
 CTGTCAAAAGGATGAGAACATCATGAGGTCATGCAGCTTTGACAATGTCTAGCCCCCAGGAGAGGGGTCAGT
 GTTTCTGGGGGACCATGCTCTAACCTCTAGTCAGGGGACCTCACCTTCTCTTCAGGTCTATCCTCATCCTACGC
 CTCCCTGGGGCTGGAGGGATCCAAGAGCTGGGATTCAAGTCTGGAGCTGAAGGGGCAAGAGAGTGG
 CAGAGTGCATCTGGGGGTTCTCCAACTCCACCAGCTCTCACCCCTTCCTGCCTGACACCCAGTGTGAGAGTGC
 CCTCCCTGAGGAAATTGAGGGCTTCCCACCTCTAACCTACTAGAAAACACACTAGAGCAGTGTCTCGTATGGTGC
 TTCCCCCATCCCTGACCTATAAACATTCCCTAAGACTCCCTCTCAGAGAGAATGCTTCACTTGGACTGGCTGG
 CTTCCTCAGACCGCCATTGAGAGGCCCTGTGGAGGGGACAAGAATGTATAGGAGAAATCTGGCTGAGTCATGGA
 TAGGTCTCTAGGGGGTGGGGTTGAGAATAGAAGGGCTGGACAGATTATGATTGCTCAGGCATACAGGTTAGCT
 CCAAGTTCCACAGGCTGCTACACAGGCCATCAAAATAAGTTCCAGGCTTGTGAGAAGACCTTGTCTCCTTAGAAA
 TGCCCCAGAAATTTCACACCTCTCGGTATCCATGGAGAGCCTGGGGCAGATATCTGGCTCATCTCTGGCTTGG
 TCCTCTCTCTCTGCTGATGTGTTGGTGGTGTGGTGGGGATGTGGATGGGGATGTCTGGCTGATGCCTG
 CAAAATTCTACCCACCCCTCTGCTTATGCTCCCTGTTGAGGGCTATGACTTGAGTTTGTGTTCCATGTTCTA
 TAGACTGGGACCTCTGCAACTGGGGCTATCACTCCCAACAGTGGATGCCTAGAAGGGAGAGGGAAGGGAGG
 AGGCATAGC

Fig. 7

HUMAN 90L PROTEIN

MRGQRKESLSDRDLGSDYDQLTGHPGPDKKALKQRFKLKKLPCCGPQALPSVSETLAAPASLRPHRPRRLDDPDGSVDDE
FELSTVCHRPEGLEQLQEQTKFTRKELQVLYRGFKNECPGIVNEENFKQIYSQFFPQGDSSYTATFLFNAFDTNHDGSV
SFEDFVAGLSVLIRGTVDRLRNWFNLYDLMNKDGCTIKEEMLDIMKSITYDMGMKGKYTYPALREEAPREHVESSFQKMDRNK
DGVVTIEEFIESCQKDENIMRSMQLFDNV

Fig. 7 Continued

RAT 9QL DNA (PARTIAL; CD: 2-775)

CCGAGATCTGGACGGCTCTATGACCAGCTTACGGGCCACCCCTCCAGGGCCCAGTAAAAAGCCCTGAAGCAGC GTTCC
 TCAAGCTGCTGCCGTGCTGGGGCCCCAAGCCCTGCCCTCAGTCAGTGAAACATTAGCTGCCCAAGCCTCCGCC
 CACAGACCCCGCCCGCTGGACCCAGACAGCGTAGAGGGATGAGTTGAATTATCACCGGTGTGTCACCGACCTGAGGGCT
 GGAACAACCTCAGAACAGACCAAGTCACACCCAGAGAGCTGCAGGTCTGTACCGAGGCTTCAAGAACGAATGCCCA
 GTGGGGATGTCAGCAGGAGAACCTCAAGCAGATTATTCAGTTCTTCCCAAGGAGACTCCAGCAACTATGCTACT
 TTTCTCTTCAATGCCTTGACACCAACCACGATGGCTCTGTCAAGTTTGAGGACTTGTGGCTGGTTGTGGTGTATTCT
 TCGGGGACCATAGATGATACTGAGCTGGCTTCAACATTATGACCTCAACAGGACGGCTGTATCACAAAGGAGG
 AAATGCCTGACATTATGAAGTCCATCTATGACATGATGGCAAGTACACATACCCCTGCCCTCCGGAGGAGGCCAAGA
 GAACACGTGGAGAGCTTCTCCAGAACAGATGGACAGGAACAAGGACGGCGTGGTGACCATCGAGGAATTATCGAGTCTT
 TCAACAGGACGAGAACATCATGAGGTCCATGCAGCTCTTGATAATGTCATCTAGCTCCCCAGGGAGGGGTTAGTGT
 TCCTAGGGTGACCAGGCTGTAGTCCTAGTCCAGACGAACCTAACCTCTCTCCAGGCCTGTCCATCTTACCTGTAC
 CCTGGGGCTGTAGGGATTCATATCTGGGCTTCAGTAGTCCAGATCCCTGAGCTAAAGTCACAAAAGTAGGCAAGAGT
 AGGCAAGCTAAATCTGGGGCTTCCAACCCCGACAGCTCTACCCCTCTCACTGATAACCTAGTGCTGAGGACACCC
 CTGGGTAGGGCCAAGTGGTCTCCACCTCTAGTCCACTCTAGAAACACATTAGACAGAAGGCTCTGTGCTATGGT
 GCTTCCCCATCCTAATCTCTTAGATTTCTCTCAAGACTCCTCTCAGAGAACACGCTCTGTCCATGTCCCCAGCTGG
 GGACATGGACAGAGCGTGTCTCTAGTTCTAGATCGCGAGCGGCCGC

RAT 9QL PROTEIN (PARTIAL)

RDLDGSYDQLTGHPPGPSKALKQRFKLKPCCGPQALPSVSETLAAPASLRPCHRPRPLPDSVEDEFELSTVCHRPEGL
 EQLQEQTKFTRRELQVLYRGFKNECPGIVNEENFKQIYSQFFPQGDSSNYATFLFNAFDTNHDGSVSFEDFVAGLSVIL
 RGTIDDRLSWAFNLYDLNKDGCTKEEMLDIMKSIYDMMGKITYPALREEAPREHVESFFQKMDRNKGVVVIEEFIESC
 QQDENIMRSRMQLFDNV

Fig. 8

MOUSE 9QL DNA (CD:181-993)

CGGGACTCTGAGGTGGGCCCTAAATCCAGCGCTCCCCAGAGAAAAGCCTTGCAGCCCCCTACTCCGGCCCCAGCCCC
 AGCAGGTGCTGCGCCGCCAGGGGCACTGTGAGGGCCCTATCTGGCCACCCGGCCCCCTCCACGGCCCAGGG
 GGAGCGGGGCCCGGGGCCATGCGGGCAAGGGCAAAGGAGAGTTGTCCGAATCCGAGATTGGACGGCTCTAT
 GACCAGCTTACGGGCACCCCTCCAGGGCCAGTAAAAAAGCCCTGAAGCAGCAGCTTCCCTAAGCTGTGCGG
 GCCCAAGCCCTGCCCCTAGTCAGTGAACATATTAGCTGCCAGCCTCCCTGGCCCCACAGACCCGCCGCTGGACC
 CAGACAGCGTGGAGGATGAGTTGAACTATCACGGTGTGCCACCGGCCAGGAGGCTGGAACAACCTCAGGAACAAACC
 AAGTTCACACCGAGAGACTGCAGGCTCTGAGAGCTCAAGAACGAAATGTCCAGGGAAATTGTCACAGGAGGAA
 CTTCAAGGAAATTATTCTCAGTTTCCCCAAGGAGACTCCAGCAACTACGCTACTTTCTCTTAATGCCCTTGACA
 CCAACCATGATGGCTCTGTCAAGTTTGAGGACTTGTGGTGTCACTGATTCTCGGGAACCATAGATGATA
 CTGAACTGGCTTCAACTTATATGACCTAACAGGATGGCTTATCACGAAGGAGGAAATCTCGACATCATGAAGTC
 CATCTATGACATGATGGCAAGTACACCTACCCCTGCCCTCGGGAGGGCCCGAGGGAACAGTGGAGAGCTTCTCC
 AGAAGATGGACAGAACAAAGGACGGCGTGGTACCAAGGAAATTCACTTGTGTCACAGGACGAGAACATCATG
 AGGTCCATGCAACTTGTATAATCTCATCTAGCTCCCCAGGGAGAGGGTTACTGTGTCCAGGGTAACCATGTC
 CCCTAGTCCAGGAAACCTAACCCCTCTCCCGGGCTGTGCTCATCTACCTGTACCCCTGGGGCTGTAGGGATTCA
 ACATCTGGCCTTAGTGTAGTCCAGATCTCTGAGCTAACGCTAACCTTCTGACTGATACCCAGTGTGAGGCTACCC
 GCGCGCAGATCCCAACCCCGACGACTCTCACCCCTTCTGACTGATACCCAGTGTGAGGCTACCCCTGGTGT
 GAACGACCAAAGTGGTCTCTGCTCCCCAGCCCACCTAGAGACCCACACTAGACGGAAATCTCTGTATGGCT
 TTCCCATCCCTGACCGCAGATTTCTCTCAAGACTCCCTCTCAGAGAATATGCTTTGTCCCTGTCCCTG
 TTTTCAGCCTAGCCTTGAGGACCTCTGTGGAGGGGAGAATAAGAACGAGACAAAATCTGGCCCTGAGCAGT
 GGTCTAGGAATCAGGCTGGAGTGGAGACAGAACGCTGGCAGGCTATGAGAGCCCCAGGTTGGCTTGT
 GTTCCACAGGCTGCTGGTCACTGAGAGTATGAGTTTCAGACTTCAAGAGGCTTATGTCATAGT
 CCAGAAATTACACATACACTCTCAGTGTCTAGGATCCAGATGTCGCTCATCCCTGAAACCTCTCCCTCT
 TCCTATGGGGAGTGGTGGCCAGGGACGATGAGTGAGCCGGTGTCCCTGGATGATGCTGTCAAGGTCC
 CCGCTGTCAGCGCTCTGGTACCCCTGGTATTCTCATGACCCCTGTCTAGATGAGAGGGTGTGGAGT
 TGCGAGCTTAGGGGAGGGAAAGAACGAGAGGGGCACTCCATCTGAACCCAGTGTGGGGCATTC
 CTGGCTCCACAATGCCCTAGGATCTTAGGGCCCCACCCACTCTTAGTGTACCCAGAGATGCTCAGAGCTCA
 CCTAGAGGGCAGGGACCATAGGATCAGGTCACCTGTCTAGCATCCGGCATGCTGTGCTTATTAAACC
 TGCTTGTGTCAGCGCCCCCTCCAGTCAGCCAGGGTGTGGGGAGGCCCCACTTCCCGCTCTGTCAGACATT
 GTTGACTGCTTGCATTGGCTCTCTACCTATTTGTATAATAAGAAAAGACACCAGATCCA
 TATGACAAAAAA
 TATGACAAAAAA

MOUSE 9QL PROTEIN

MRGQGRKESELSESRLDLDGSYDQLTGHPPGPSKKALKQRFKLKPCCGPQALPSVSETLAAPASLRPHRPRPLDPDSVEDE
 FELSTVCHRPEGLEQLQEQTAKFTRELQVLYRGFKNECPSGIVNEENFKQIYSQFFFQGDSSNYATFLFNADTNHDGSV
 SFEDFVAGLSVILRGTFIDRLNWFNLYDLNKDGCTKEEMLDIMKSIYDMMGKYTYPALARREEAPREHVESFFQKMDRK
 DGVTIEEFIESCQQDENIMRSMLQFDNVI

HUMAN 9QM DNA (CD:207-965)

CTCACCTGCTGCCAGTAGTGTCCCTCTCTGCTCCAGGACCTCCGGTAGACCTCAGACCCCCGGGCCATTCCCAGACTCA
 GCCTCAGCCCCGACTTCCCAGCCCCGACAGCACAGTAGGCCGCAGGGGGCGCCGTGTGAGGCCCTATCCCGGCCACC
 CGGGCGCCCCCTCCCACGGCCCGGGCGGGACCGGGCGCCGGGGCATGCCGGGCAGGGCGCAAGGAGAGTTGTC
 ATTCCCCGAGACCTGGACGGCTCTACGACAGCTCACGGGCCACCCCTCAGGGCCACTAAAAAGCGCTGAAGCAGCGA
 TTCCCTCAAGCTGCTGCCCTGCTGCCGGCCCAAGCCCTGCCCTCAGTAGTGAAGAACAGCGTGGACGATGAATTGAATT
 GTCCACCGTGTGTACCCGCCCTGGAGCTGGAGCAGCTGCAGGAGCAAACCAAATTACCGCGCAAGGAGTTGCAAGGTC
 TGTACCGGGGCTCAAGAACAGATGTCACCGCGAATTGTCATGAGGAGAACTTCAGCAGAGATTACTCCAGTTCTT
 CCTCAAGGAGACTCCAGCACCTATGCCACTTTCTTCATGCCCTTGACACCAACCATGATGGCTGGTCAGTTTGA
 GGACTTTGTGGCTGGTTGTCCGTGATTCTCGGGGAACTGTAGATGACAGGCCATTGGGCCCTCAACCTGTATGACC
 TTAACAAGGACGGCTGCATCACCAAGGAGGAATTGCTTGACATCATGAGTCATCTATGACATGATGGCAAGTACAG
 TACCCCTGCACTCGGGAGGGGCCAAGGAAACAGTGGAGAGCTTCCAGAAGATGGACAGAACAAAGGATGGTGT
 GGTGACCATGAGGAATTGATTGAGTCCTGCAAAAGGATGAGAACATCATGAGGTCCATGCAGCTTGTGACAATGTC
 TCTAGCCCCCAGGAGAGGGGTCAGTGTCTGGGGGACATGCTCTAACCTCTAGTCCAGGCGGACCTCACCTTCTC
 TTCCCAGGTCTATCCCTCATCCCTACGCCCTGGGGCTGGAGGATCCAAGAGCTGGGATTTCAGTAGTCCAGATCTC
 TGGAGCTGAAGGGGCCAGAGAGTGGCAGAGTGCATCTCGGGGGGTGTTCCCAACTCCACCAGCTCTCACCCCTTCTC
 GCCTGACACCCAGTGTGAGAGTGGCCCTCTGTAGGAATTGAGCGGTTCCACCTCTAACCTACTCTAGAAACAC
 TAGAGCGATGTCTCCGTATGGCTCTCCCCATCCCTGACCTCATAAACATTCCCTAAGACTCCCTCTCAGAGAG
 AATGCTCATTCTGGCACTGGCTGGCTCTCAGACCCAGCCATTGAGAGGCCCTGAGGGGGGACAAGAATGTATAGGG
 AGAAATCTGGGCTGAGTCATGGATAGGCTCAGAGGGGGGGGGGGTGGAGAATAGAAGGGCTGGACAGATTGAG
 TTGCTCAGGCATACCAGGTTAGAGCTCAAGTCCACAGGGCTGCTACCCACAGGCCATCAAATAAATAGTTCCAGGCTT
 TGCAAGAACCTTGTCTCTTAGAAATGCCAGAAATTTCACCCCTCTCGGTATCCATGGAGAGCCTGGGGCCAG
 ATATCTGGCTCATCTGGCATTGCTCTCTCCCTGCTGATGTGTTGGTGGTGTGGTGGGGGGAAATGTGGA
 TGGGGGATGTCCTGGCTGATGCCAAATTCTACCCACCTCTGGCTTATGCTCCCTGTTGAGGGCTATGACT
 TGAGTTTTGTCTCCCATGTTCTATAGACTGGACCTCTGAACTTGGGCTATCAGTCCACAGTGGATGCC
 TAGAACGGAGAGGAAGGAGGGAGGCAGGATAGC

Fig. 10

HUMAN 9QM PROTEIN

MRGQGRKESLSDSRDLDGSYDQLTGHPPGPTKKALKQRFLKLLPCCGPQALPSVSENSVDEFELSTVCHRPEGLEQLQE
QTKFTRKELQVLYRGFKNECPGIVNEENFKQIYSQFFPQGDSSTYATFLFNAFDTNHDGSVSFEDFVAGLSVILRGTVD
DRLNWAFNLYDLNKDGCTKEEMLDIMKSIYDMMGKYTPALREEAPREHVESFFQKMDRNKDGVVTIEEFIESCQKDEN
IMRSMQLFDNVI

Fig. 10 Continued

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RAT 9QM DNA (CD:214-972)

CTCACTTGTGCCCCAGGCTCCCTGGCTCTGGCCCAAGGACTCTGAGGTGGGCCCTAAAACCCAGCGCTCTCTAAAGAAAAG
CCTTGCAAGCCCCCTACTCCCGGCCCAACCCAGCAGGTCGCTGCAGCGGCCAGGGGGCGCTGTGTGAGCGCCCTATTCT
GGCCACCCGGCGCCCCCTCCCACGGCCCAAGGGAGCGGGCGCCGGGGCATCGGGGCAAGGCAGAAAGGGAGGT
TTGTCCGAATCCCGAGATCTGGACGGCTCCATTGACCAGCTTACGGGCCACCCCTCAGTCAGTGAAACAGCGTAGAGGATGAGT
GCAGCGTTCTCAAGCTGCTGGCTCGGGCCCAAGGCCCTGCCCTCAGTCAGTGAAACAGCGTAGAGGATGAGT
TTGAATTATCCACGGTGTGACCGACTGAGGGCTGGAACAACTCCAGGAACAGACCAAGTTCACACGGCAGAGAGCTG
CAGGTCTGTACCGAGGCTCAAGAACGAAATGCCAGTGGGATTGTCAACGAGGAGAACCTCAAGCAGATTTATTC
GTTCTTCCCAAGGAGACTCCAGCAACTATGCTACTTTCTCTTAATGCCCTGACACCAACCACGATGGCTGTCA
GTTTGAGGACTTGTGGCTGGTTGTGCGTGTATTCTCGGGGACCATAGATGATAGACTGAGCTGGCTTCAACTTA
TATGACCTCAACAAGGACGGCTGTATCACAAAGGAGGAATGCTTGACATTATGAGTCCATCTATGACATGATGGCAA
GTACACATACCCCTGCCCTCCGGAGGAGGGCCAAGAGAACAGCTGGAGAGCTTCCAGAAGATGGACAGGAACAGG
ACGGCGTGGTGAACATCGAGGAATTATCGAGTCAGGACGAGAACATCATGAGGTCATGCAGCTTTGT
AATGTCATCTAGCTCCCAGGGAGAGGGTGTAGTGTCTAGGGTGTAGCTCAGTCAGCAGAACCTAA
CCCTCTCTCCAGGCTGTCTCATCTTACCTGTACCCCTGGGGCTGTAGGGATTCAATATCTGGGCTTCAGTAGTC
CAGATCCCTGAGCTAAGTCACAAAGTAGGCAAGAGTAGGCAAGCTAAATCTGGGCTTCACCCCGACAGCTC
ACCCCTCTCAACTGTACCTAGTGTGAGGACACCCCTGGGTAGGGACCAAGTGGTTCTCCACCTTCTAGCTCCACTC
TAGAACCCACATTAGACAGAAGGTCTCTCTATGGTGCTTCCCATCCCTAACTCTCTAGATTCTCTCAAGACTCCC
TTCTCAGAGAACAGCTGTCTCATGTCCCCAGCTGGCTCTCAGCCTAGCCTTGAGGGCTGTGGGGAGCGGGGAC
AAGAACAGAAAAGTCTGGCCCGAGCCAGTGGTTAGGCTCTAGGAATTGGCTGGAGTGGAGGCCAGAACGCTGGG
AGATGATGAGAGGCCAGCTGGCTGTACTGCAGGTTCCGGGCTACAGCCCTGGGTAGCAGAGTATGAGTCCAGA
CTTTCAGAGGTCTTAGCAATGTCCAGAAATTACCGTACACTCTCAGTGTCTTAGGAGGGCCGGATCCAGATG
TCTGGTTCATCCCTGAATCTCTCCCTCTTGTCTGCTGTATGGTGGAGTGGTGGCCAGGGGAAGATGAGTGGTGTCCC
GGATGATGCTGTCAAGGCCACCTCCCTCCGGTGTCTCATGACAGCTGGTTCTCCATGACCCCTATCTAGA
TGTAGAGGCATGGAGTGTAGTCAGGGATTCCGAACATTGAGTTTACACTCTCTCTAGTGGCTGCCCTAGGGAAATGG
AAGAACCCAGTGTGGGGCACCCATTAGAAATCTTGCCGGCTCACAATGCCCTAGGGCTCCCTAGGGTACCCGTC
CCTCTGTTAGTCTACCCAGAGATGCTCTGAGCTCACCTAGAGGGTAGGGAGCTAGGGCTCCAGGTCAACCTCTCCAG
GTCAGCACCCCTGCGATGCTGTCTCTCATTAACAAACCTGCTGTCTCTCTGCGCCCTTCAGTCAGGCCAGGGT
CTGAGGGGAAGGGCTCCCGTCTCCATCGTACGACATGGTACTGCTTTGCTATCTATCTATTTG
TAAAATAAGACATCAGATCCAATAAAACACACGGCTATGCACAAAAAAAAAAAAAA

RAT 9QM PROTEIN

MRQQGRKESLSESRDLDGSYDQLTGHPPGPSKKALKQRFKLKPCCGPQALPSVSENEFELSTVCHRPEGLEQLQE
QTKFTRRELQVLYRGFKNECPGIVNEENFKQIYSQFFPQGDSSNYATFLFNADFTNHDGSVSFEDFVAGLSVILRGTD
DRLSWAFNLYDLNKDGCTKEEMLDIMKSITYDMGMKYTYPALREEAPREHVESFFQKMDRNKDGVVTIEEFIESCQDEN
IMRSMQLFDNVI

Fig. 11

HUMAN 9QS DNA (CD:207-869)

CTCACCTGCTGCCCTAGTGTCCCTCTCCTGCCTCAGGACCTCCGGTAGACCTCAGACCCCAGGCCATTCCCAGACTCA
 GCCTCAGCCGGACTTCCCAGCCCCGACAGCACAGTAGGCCAGGGGGCGCCGTGTGAGGCCCTATCCGGCCACC
 CGCGCCCCCTCCCACGGCCGGGGAGCGGGGCGCCGGGGCATGCCGGCCAGGGCCGAAGGAGAGTTGTCCG
 ATTCCCCGAGACCTGGACGGCTCCTACGACAGCTCACGGACAGCGTGGACGATGAATTGAAATTGTCACCGCTGTAC
 CGGCCTGAGGGTCTGGAGCAGCTGCAGGAGCAAACCAAATTCACGCGAAGGAGTTGCAGGTCTGTACCGGGCTCAA
 GAACGAATGTCCAGCGGAATTGCAATGAGGAGAACCTCAACGAGATTACTCCAGTTCTTCCTCAAGGAGACTCCA
 GCACCTATGCCACTTTCTTCAATGCCCTTGACACCAACCATGATGGCTCGTAGTTGAGGACTTTGTGGCTGGT
 TTGTCCGTGATTCTCGGGGAACGTAGATGACAGGCTTAATTGGGCCAACCTGTATGACCTAACAGGACGGCTG
 CATCACCAAGGAGGAATGCTTGACATCATGAAGTCCATCTATGACATGATGGCAAGTACACGTACCCCTGACTCCGG
 AGGAGGCCAAGGGAACACGTGGAGAGCTTCCAGAAGATGGACAGAACAAAGGATGGTGTGGACATTGAGGAA
 TTCATTGAGTCTGTCAAAGGATGAGAACATCATGAGGTCCATGCAGCTTGTACAATGTCATCTAGCCCCCAGGAGA
 GGGGGTCAGTGTCTGGGGGACATGCTAACCTAGTCCAGGCGGACCTCACCCCTCTTCCAGGTCTATCCT
 CATCCCTACGCCCTGGGGTGGAGGATCCAAGAGCTGGGATTCACTAGTCCAGATCTCTGGAGCTGAAGGGGCC
 AGAGAGTGGCAGACTGCATCTGGGGGTGTTCCAACCTCCACAGCTCTCACCCCTCTGGCTGACACCCAGTGT
 TGAGAGTGGCCCTCTGTAGGAATTGAGCGGTTCCACCTCTACCTACTCTAGAAACACACTAGAGCGATGTCTCT
 GCTATGGTCTCCCCATCCGTACCTCATAAACATTCCCTAACAGACTCCCTCTCAGAGAGAATGCTCCATTCTGG
 CACTGGCTGGCTTCAGGACGCCATTGAGAGCCCTGTGGGAGGGGACAAGAATGTATAGGGAGAAATCTGGGCTG
 AGTCATGGATAGGTCTAGGGAGGTGGGTGGGTGAGAATAGAAGGGCTGGACAGATTATGATGTCTCAGGCATACCA
 GGTTAGCTCAAGTCCACAGGTCTGCTACCCAGGCCATAAATATAAGTTCCAGGCTTGTGAGAAGACCTTGTG
 TCCCTAGAAATGCCAGAAATTCCACACCCCTCTGGTATCCATGGAGAGCCCTGGGGCAGATATCTGGCTCATCTC
 TGGCATGGCTCTCTCCCTCTGATGTGGGTGGTGGTGGGGAAATGTGGATGGGGATGTCTGG
 TGATGCTGCCAAATTCTATCCACCCCTCTGGTATCGCCCTGTTTGAGGGCTATGACTTGTAGTTTCTTCCC
 ATGTTCTATAGACTGGGACCTCTGAACTTGGGCTATCACTCCCCACAGTGGATGCCCTAGAAGGGAGAGGAA
 GGAGGGAGGCAGGCATAGC

Fig. 12

MONKEY 90S DNA (CD:133-795)

CCACCGCGTCCGCCACCGCTCCGCGGACCGCTGGGTGCACTAGGCCGCCAGGGGGCCTGAGGCCCTATCCCG
GCCACCCGGCCCCCTCCACGGGACCGGGGGAGCAGGGGGCATGCCGGGGCAGGGGCCAGGGGCCAAGGAGAGTT
TGTCCGATTCCCAGACCTGGACGGATCCTACGACCAAGCAGCTACGGACAGCGTGGAGGTGAATTGAAATTGTCACCGTG
TGTACCCGGCTAGGGCTGGACAGCTCAGGACAAACAAATTACAGCGCAAGGAGTTGCAAGGCTCTGACCGGG
CTTCAGAACGAAATGTCGAGCGGAATTGTCATGAGGAGAACTTCAGCAAATTACTCCAGTTCTCTCAAGGAG
ACTCCAGCACCTATGCCACTTTCTCTCAATGCCTTGACACCAACCATGATGGCTGGTCAAGTTGAGGACTTTGTC
GCTGGTTGTCGTGATTCTCGGGAACTGTAGATGACAGGCCAATTGGGCCCTCAACTGTATGACCTCAACAAGGA
CGGCTGCATACCAAGGAGGAATGCTTGACATCATGAGTCATGACATGATGGCAAGTACACATACACCTGAC
TCCGGGAGGAGGCCAACGGGACATGTTGGAGAACTTCTTCAGAAAGATGGCAGAAACAAGGATGGCTGGTGACATT
GAGGAATTCTTGTAGTCTGTCAAAGGATGAGAACATCATGAGGTCTATGAGGCTCTTGTACAATGTCATCTAGCCCC
AGGAGAGGGGGTCAGTGTTCCTGGGGGACCATGCTAACCCCTAGTCAGGTGACCTCACCTCTCTCCCCAGGTC
TATCTTGTCTTAGGCCTCCCTGGGGCTGGAGGATCCAAGAGCTGGGATTCTAGTAGTCCAGATCTCTGGAGCTGAA
GGGGCCAGAGAGTGGCAGAGTCATCTGGGGGTGTTCCAACCTCCACAGCTTCAACCGCTTCTGCTGACACC
CAGTGTGAGAGTGCCTCTCTGTAGGAACCTGAGTGTGTTCCCCACCTCTACCCCCACTCTAGAACACACTAGACAGAT
CTCTCGTCTATGGTGTCTCCCCATCCCTGACTCTATAAACATTCTCTAACACTCTCTCTAGAGAGAAATGCTCCA
TTCTTGGCAGCTGGCTTCTCAGACCGCCCTTGAGACCCCTGTGGAGGGGACAAGAATGTATAGGGAGAAATCT
TGGGCTGAGTCATGGATAGGTCTTAGGAGGTGCTGGGGTTGAGAAATAGAAAGGCCCTGGACACAATGTGTTGCTCAG
GCATACCAAGTTAGTCACAGGCTCTGACACAGGCCATCAAATAAGTGTGCTTCAGGCTTGTGAGAAG
ACCTTGTCTCTGGAAATGCCCAAGATACTTCCATACCCCTCTGATATCCATGGAGAGCTGGGGCTAGATATCTGG
CATATCCCTGGCATTGCTTCTCTCTCTGCTGATCTGGTGTGGGGTTGAGGCCAGGGGAATGTGGATAGGAGAT
GTCCTGGCAGATGCTGCCAACAGTTCTACCCACCCCTCTGCTCATGCCCTGTGTTTGTGGAGGCTGTGACTTGTG
TGTGTTCTCATGTTCTCTATAGACTGGACCTTCTGAACTTGGGCTATCCTACCTCCACAGTGGATGCTTGTGAAAGGG
AGAGGGAGGGGGAGGGCAGGCAAGTGCATCTGAAACCCAGTGTGGGGCATCTACTAGGATCTTCATCAACCCGGCTCT
CCCCAACCCCCCAGATAACCTCTCAGTCTCCAGTGTCTCTGCTCATCTACCTACCCAGAGATGCCCTTCTAGC
ACACTCAGAGGGCAGGGACCATAGGACCCAGGTTCAACCCCTAGTCAGCAGGCCATGCCCTACCCCTTCTAGC
ACCTGCTGTCCTCATTGCTTACCCCTCCAGTCAGCAGAACATGTCAGGGGGAGGGGCCAGAGAGCCCCCTTCTC
AGAAGACTGTGACTGCTTGTGATTTGGCTCTCTATATTTGAAAATAAGAACATACCCAGATCTAATAAAACA
CAATGGCTATGCAAAAAAAAAAAAAAA

MONKEY 90S PROTEIN

MRRGQGRKESLSDSRDLDGSYDQLTDSVEDEFELSTVCHRPEGLEQLQEQTKFTRKEVLQYRFGFKNECPFGIVNEENFKQ
IYSQFFFQGDSSTYATFLNNAFDTNHDGSVSFEDFVGALSVILRGTVDDRLNWAFNLYDLNKDGCGITKEEMLDIMKSIIYD
MMGKYTYPALREEAPREHVNENF0KMDRNRKNDGVTTIEFIESCQDENIMRSMOLFNDNVI

Fig. 13

RAT 9QC DNA (CD:208-966)

TCGCTGCCAAGGCCTCGCTCCGTCCCCAGGACTCTGAGGTGGGCCCTAAACCCAGCGCTCTCTAAAGAAAAGCCTTGC
 CAGCCCCCTACTCCCGGCCCCAACCCAGCAGGTGCGCTGCCGCCAGGGGCCCTGTGTGAGCGCCCTATTCTGGGCC
 CCGGCGCCCCCTCCCACGGGCCAGGGAGCGGGGCCGGGGGCCATGCGGGCCAAGGCAGAAAGGAGAGTTTCTC
 GAATCCGAGATCTGGACGGCTCTATGACCAGCTTACGGGCCACCCCTCAGGGCCAGTAAAAAGCCCTGAAGCAGCG
 TTCCCTCAAGCTGCTGCCGTGCTGGGGGCCCAAGCCCTGCCCTAGTCAGTGAACACGGTAGAGGATGAGTTGAT
 TATCCACGGTGTGTCACCGACCTGAGGGCTGGAACAACCTCAGGAACAGCAAGTCACCGCAGAGGAGCTGCAGGTC
 CTGTAACGGGCTTCAGAACAGAATGCCCACTGGGATTGTCAACGAGGAGAACTTCAGCAGATTATTCTCAGTTCTT
 TCCCCAAGGAGACTCCAGCAACTATGCTACTTTCTCTCAATGCCCTTGACACCAACCACGATGGCTCTGTCAGTTTG
 AGGACTTTGGCTGGTTGCGTGTCTCGGGGACCATAGATGATAGACTGAGCTGGGCTTCACCTTATATGAC
 CTCAACAAGGACGGCTGTATCACAAAGGAGGAATGCTTGACATTATGAAGTCCATCTATGACATGATGGGCAAGTACAC
 ATACCCCTGCCCTCGGGAGGGAGGCCAACAGAACACGTGGAGAGCTTCTCCAGAAGATGGACAGGAACAAGGACGGC
 TGTTGACCATCGAGGAATTATCGAGTCCTGTCAACAGGAGGAAACATCATGAGGTCCATGCCACCTCTCACCCCTCTC
 AACTGATACCTAGTGTGAGGACACCCCTGGTGTAGGGACCAAGTGGTTCTCCACCTCTAGTCCACTCTAGAAACAC
 ATTAGACAGAAGGTCTCTGTATGGTGTCTCCCATCCCTAATCTCTAGATTTCCTCAAGACTCCCTCTCAGAGA
 ACACGCTGTGCCATGCCAGCTGGCTTCAGCCTAGGCCCTTGAGGGCCCTGTGGGGAGGGGACAAGAACAG
 AAAAGCTTGGCCCGAGCAGTGGTTAGGTCTAGGAATTGGCTGGAGTGGAGGCCAGAAAGCCTGGGAGATGATGAG
 AGCCCAGCTGGGCTGTCACTGCAGGTTCCGGGCTACGCCCTGGGTCAAGCAGAGTATGAGTTCCAGACTTTCCAGAA
 GGTCTTCTAGAACATGCCAGAAATTACCCGTACACTCTCAGTGTCTTAGGGAGGGCCGGGATCCAGATGTCTGGTCT
 CCCCTGAATCTCTCCCTCTTGTCTGTATGGTGGAGGTGGTGGCCAGGGAGAGATGAGTGGTGTCCGGATGATGCC
 TGTCIAAGGTCCCACCTCCCTCGGTGTTCTCATGACAGCTGGTCTCCATGCCCTATCTAGATGAGGCA
 TGGAGTGAATGCCAGGGATTTCCTGAATTCTGAGTTTACCACTCTCTAGTGGCTGCCCTAGGGGAATGGGAGAACCCAG
 TGTGGGGCACCCATTAGAATCTTGCCTGGCTCTCACATGCCCTAGGGTCCCTAGGGTACCCGCTCCCTGTGTTA
 GTCTACCCAGAGATGCTCTGAGCTCACCTAGGGTAGGGACGGTAGGGCTCCAGGTCAACCTCTCCAGGTCAGCC
 TGCCATGCTGCTGCTCTCATTAACAAACCTCTGTCTCTCTGCCCTTCTCAGTCAGCCAGGGTCTGGGGAA
 GGGCTCCCGTTCCCATCCGTCAAGACATGGTGTACTGCTTGATTTGGGCTCTCTATCTATTTGTAAGA
 CATCAGATCCAATAAAACACGGCTATGCACAAAAAAAAAAAAAA

RAT 9QC PROTEIN

MRCQGRKESLSESRDLDGSYDQLTGHPPGPSSKKALKQRFLKLLPCCGPQALPSVENSVEDEFELSTVCHRPEGLEQLQE
 QTKFTRELQVLYRGFKNECPGIVNEENFKQIYQSFFFQGDSSNYATFLNFAFDTNHDGSVFSFEDFVAGLSVLRTID
 DRLSWAFNLYDLNKDGCTKEEMLDIMKSITYDMMGKYTPALREEAPREHVESFFQKMDRNKDGVVIEEFIESCQQDEN
 IMRSMQLSPLLN

Fig. 14

RAT 8T (9Q SPLICE VARAIANT) DNA (MAY NOT BE FULL LENGTH, CD: 1-678)

ATGAACCACTGCCCTCGCAGGTGCCGGAGCCCGTGGGAGCAGCTGATCTCTACCACTGGTAACTGGGTCGCT
 GTGCCAGACAGCTAGAGGATGAGTTGAATTATCCACGGTGTGTCACCGACCTGAGGGCCTGAAACAACCTCCAGAAC
 AGACCAACTTCACACGCAGAGACTGCAGGTCTGTACCGAGGCTCAAGAACGATGCCAGTGGGATTGTCACAGAG
 GAGAACCTCAAGCAGATTATTCTCAGTTCTTCCCCAAGGAGACTCCACAACTATGCTACTTTCTCTCAATGCC
 TGACACCAACACAGATGCCCTGTCAAGTTTGAGGACTTTGCGCTGGTTGCGTGAATTCTCGGGGACCATAGATG
 ATAGACTGAGCTGGGCTTCACCTTATGACCTCAACAGGACGGCTGTACAAAGGAGGAAATGCTTGACATTATG
 AAGTCACATATGACATGATGGGCAAGTACACATAACCCCTGCCCTCCGGAGGGCCCAAGGAAACACGTTGGAGAGCTT
 CTTCCAGAAGATGGACAGAACAGGACGGCTGGTACCATCGAGGAATTCTCGAGTCTTGCAACAGGACGAGAAC
 TCATGAGGCCATGAGCTTTGATAATGTCATCTAGCTCCCAGGGAGGGGTTAGTGTGTCCTAGGGTACAGGC
 TGTAGTCCTAGTCCAGACGAACCTAACCTCTCTCAGGCCCTGTCTCATCTTACCTGTACCCCTGGGGCTGTAGGG
 TTCAATATCCTGGGGCTTCAGTAGTCAGATCCCCTGAGCTAACAGTAGGCAAGAGTAGGCAAGGCTAAATCTG
 GGGCTTCCAACCCCCAGCTCTCACCCCTCTCAACTGATACCTAGTGTAGGACACCCCTGGTGTAGGGACCAAG
 TGGTTCTCACCTCTAGTCCACTCTAGAAACACATTAGACAGAAGGCTCCAGTGTACGGTCTTCACCCATCCCTAA
 TCTCTTAGATTTCCTCAAGACTCCCTCTCAGAGAACACGCTCTGTCATGCCCCAGCTGGCTTCTCAGCCTAGCCTT
 TGAGGCCCTGGGGAGGGGGACAAGAACAGAGAAAATCTGGCCCGAGCTAGTGGTTAGGCTCTAGGAATTGGC
 TGGAGTGGAGGCCAGAACGCTGGGAGTATGAGGAGGCCAGCTGGGCTGTACTGCAGGTTCCAGGGCTACAGCCT
 GGGTCAGCAGAGTATGAGTTCCAGACTTCCAGAGGCTCTAGCAATGTCAGAACCTACACTCTCAGTG
 TCCCCGGATGATGCCCTGTCAAGGCTCCACCTCCCTCCGGCTGTCTCATGACAGCTGTTGGTCTCCATGACCCCTATC
 TAGATGTAAGGCCATGGAGTGTAGTCAGGGATTCCGAACCTTGAGTTTACCACTCCCTCTAGTGGCTGCCTAGGGAA
 TGGGAAGAACCCAGTGTGGGGCACCCATTAGAATCTTGCCGGTCTCACAAATGCCCTAGGGTCCCTAGGGTACCC
 GCTCCCTGTGTTAGTCTACCCAGAGATGTCCTGTAGCTCACCTAGAGGGTAGGGACGGTAGGCTCCAGGTCAACCTCT
 CCAGGTCAAGCACCCCTGCCATGCTGCTCTCATTAACAAACCTGCTGTCTCTGCGCCCTCTCAGTCAGCCA
 GGGCTGAGGGGAAGGGCTCCCGTCCATCGTCAGACATGGTTGACTGCTTGCATTGGCTCTTCTATCTAT
 TTGTAAGAACATGATCCAATAAAACACAGCCTATGCAACAAAAAAAAAAAAAA

RAT 8T (9Q SPLICE VARAIANT) PROTEIN (MAY NOT BE FULL LENGTH)

MNHCPRRCRSPLGQAARSLYQLVTGSLSLPSDEDEFELSTVCHRPEGLEQLQEQTKFTRRELQVLYRGFKNECPGIVNE
 ENFKQIYSQFFPQGDSSNYATFLFNADFDTNHDGSVSFEDFVAGLSVILRGITDDRLSWAFLNLYDLNKDGCTKEEMLDIM
 KSIYDMMGKYTYPALREEAPREHVESFFQKMDRKNKGVVTTIEFIESCQQDENIMRSQMLFDNVI

Fig. 16

>human KChIP3
MQPAKEVTKASDGSLLGDLGHTPLSKKEGIKWQRPLSRQALMRCCLVWKWILSSTAPQGSDSSD
SELELSTVRHQPEGLD
QLQAQTKFTKKELQSLYRGFKNECPTGLVDDETFKLIYAQFFPQGDATTYAHFLFNAFDADGNG
AIHFEDFVVGLSILLR
GTVHEKLRWAFNLYDINKDGYITKEEMLAIMKSIYDMMGRHTYPILREDAPAEHVERFFEKMD
RNQDGVVTEEFLEACQ
KDENIMSSMQLFENVI

Fig.16 Continued

09570756 - 092700

RAT P19 DNA (FIRST PASS, PARTIAL; CD:1-330)

TTTGAGGACTTGTGGTGGCTCTCATCCTGCTTCGAGGGACCGTCCATGAGAAGCTCAAGTGGGCCTCAATCTCTA
CGACATCAACAAGGACGGTTACATCACCAAAGAGGAGATGCTGCCATCATGAAGTCCATCTACGACATGATGGGCCGCC
ACACCTACCCATCCTGCGGGGAGGACGCACCTCTGGAGCATGTGGAGGGTCTTCCAGAAAATGGACAGGAACCAGGAT
GGAGTAGTGACTATTGATGAATTCTGGAGACTTGTCAAGAGCAGAGAACATCATGAGCTCCATGCAGCTGTTGAGAA
CGTCATCTAGGACATGTAGGAGGGGACCCCTGGGTGGCCATGGTTCTCAACCCAGAGAACGCTCAATCCTGACAGGAGAA
GCCTCTATGAGAACATTTCTAATATATTGCAAAAGTG

RAT P19 PROTEIN (PARTIAL)

FEDFVVLISLLRGTVHEKLWAFNLYDINKDGYITKEEMLAIMKSIYDMGRHTYPILREDAPLEHVERFFQKMDRNQD
GVVTIDEFLTCQKDENIMSSMQLFENVI

Fig. 17

MOUSE P19 DNA (CD: 49-819)

CGGGCTGCAAAGCGGGAAAGTTAGTGACGGTCCCTTCAGCAGCAGAGATGCAGAGGACCAAGGAAGGCCGTGAAGGCATC
 AGATGGCAACCTCCCTGGGAGATCTGGGCCATACCAACTGAGCAAGAGGAAAGCATCAAGTGGCAAAAGGCCACGGTCTCA
 CCCGCCAGGCCCTGATGCGTTGCTGCTTAATCAAGTGGATCCTGTCAGTGCCTGCCACAAGGCTCAGACAGCAGTGAC
 AGTGAACGGAGTTATCCACCGTGCGCCATCAGCCAGAGGGCTGGACCAGCTCAAGGCTCAGACCAACTTACCAAGAA
 GGAGCTGCACTCCCTTACCGAGGCTCAAGAATGAGTGTCCCACAGGCTGGGGATGAAGACACCTTCAAACCTATT
 ATTCCCAAGTTCTCCCTCAGGGAGATGCCACACCATGACACTTCTCTTCAATGCTTGTGATGGAAACGGG
 GCCATCCAATTGAGGACTTGTGGTTGGGCTCTCCATCTGCTTCAGGGACGGTCCATGAGAACTCAAGTGGCCT
 CAATCTCATGACATTAACAAGGATGGTGATCACCAAGGAGGAGATGCTGGCCATCATGAAGTCCATCTACGACATGA
 TGGGCGGCCACACCTACCCATCCTGCGGGAGGATGCACCCCTGGAGCATGTTGAGGGTCTTCAGAAAATGGACAGG
 AACCAAGGATGGAGTGGTGCACATTGATGATTTCTGGAGACTTGTGAGAAGGATGAGAACATCATGAACATCCATGCAGCT
 GTTGTGAGAACGTCATCTAGGACATGTTGGGGGGACCCCAGTGGTCTTGCTTCAACCCAGAGSAGCCTCAATCTGA
 CAGGAGAACGCTCATGAGAAACATTTCATAATATATTTGCAAAAGTGGAGCTTACTTCAAGACACAGCACCGT
 CACACACAGACACAGACATACAGACACACACACACACACACATGGTCTCTGGCTTGGCAAGGAAGTGGCAGCC
 AGAAGGCACCCCCGCTATTCTTAGGTCAATAAAAAGGCTGCTCTGGGATGGCAGCCCTGGCTAGATGTTACCCACA
 AGGAACCTCAGAGATCGAGAGGACCGGGTCAAAAGCTAAGGCTCTGTGTCTTCTACCACTGGGAGATCAAACATAC
 TCCCTGCCTATGGACCCATGCTCTTAGGAAGCTTCCAGAAAACCTCAAGGGACAAAGAGGGAGAGGTCTATAGGAAGAA
 ATGGTTTGGAAAGCTGGGCTTGACGGCTTATGCTAATGTCACCTGGGTCTCTGGAAACCCGACTGCCAGGCTACCTACTA
 TGCCGTGAGCTTAGATGAGTGGGGCCATTGGACTAAGACCTCTGTAAAGGTGGGGCAGGATTGAGGTTTGGAGAAA
 CTGAGGAAACAATTGTCATACCACTGGTGAAGACTGCTGCCAGTGGGAATGTGCTGGTGGAGATTTCCCAACTTC
 CAGCACCAGGATGGCCTCTCAAGGCTCTTGTGATTCCCTGGGAGATCAGCTGGCTCATAGACTGACAAACAGGGAAAC
 TGGGCTGAAATGGGAGGTTGGTAGGGGCATCCCCCTCTTCTGGCAGCTTCCCTGGCAGCTCCCTTAACACAGTG
 GATGCCACACCTCTGTGGCTGCCCTTGACAGACTCATCCGCCAAAGACAAAAAGCACTAACTCTAGCAGCTCAG
 GCCAAGGCCACAAGGGAAAGGCCCTGGGCTCTGCAAGGCTGATCTAGTGGCCAGGAAGACGCTCAGACATCCATCTGT
 CCTCGGAGCCTGGGGCTCTCACAGCCCTTCCAGGCCAGCTGCCAACATTCAAAGCACAAACCTGGGATCTGT
 TGCTGGGCTGCCCTGGGATTGAGGCCACTGTTAACCTAAAGCTGGAGCTAGCCCTGGGGCTGGGACCTGTGAC
 CAGGCAAGCTCAGCAGACCTCAGGAGGAGAGAGCTGTTCTGCTGCCCTCCAGGCCAGGCTCGCCAGAAGGAACAGTGT
 CCAAGGAAGCATGTTCTGGAGGAACATCCCCAACAAACTACATTCCATCATCTGAAGCCGGCTCTGCTCAGGCCCTG
 CTCTGAAAGTCCAGGTGTTCTGGAGGAACAGGCCAGGCCAACATAAGGGAGCTTGTAGAGGAAGGACAGGGTACACA
 CCCCTATACACAGGTGGACCCCCCTCTGGGACTGTACTGACCCCATCTCCATCTGACGGGGGCTTCTTACCGA
 TCTACAGACCAAGGCTCAGGACAGGACACAGACTGGCCGATGTCCTAGGAGAAGCTGCTGACCTTCCCATGAGGCTCTG
 GAAAAGCCAAGGCCACGGAAAAGGCCACCAACTCTAACCTGTCATGCCCTAGGCTGACGCCAACCTGGAG
 GGGTCTGCTCCCTTGCAGGGACACAGACTGGCCGATGTCCTAGGAGAAGCTGCTCCCTGGGTGAGCTGGAG
 GGTGTTCTGTCAGGCCACCAATATTCAAGTCTCATATATTAAATAAAAAGAAACTTGACAAAGGAAAAAA
 AAAA

Fig. 18

0002600-25207960

>AI 352454 (partial) cds = 1-339
 CACGAGGTGAAAGCATTCGGCTCAGCTGGAGGAGGCCAGCTCTACAGGCCTTCCCTGT
 ACGCTCAGAACACCAAA
 CGCGCAGCATTTAAAGACCGGCTCATGAAGCTCTGCCCTGCTCAGCTGCCAAAACGTCGTCTC
 CTGCTATTCAAAACAGGG
 TGGAAAGATGAAACTGGAGATGGCCACCGTCAGGCATGGCCGAAGCCCTTGAGCTTCTGGA
 AGCCCCAGACCAAATTAC
 AAGAAAGAGCTTCAGATCCTTACAGAGGATTTAAGAACGTAAGAACCTTCTTTGACTTT
 ACCTTCACACAAATTCCCA
 GAGGAGCATTGAGAAAATGAgagaaaaaggggaaaatccattctatgagaacccatcatatgtatattcataact
 gatccctccagataggaaatataatcgtatctgtggacttgaatctctgtggcacacccatgtggcatactgttaatt
 gccccattaaacaaanagtttgagaaaaaaaaaaaaaaaaaaaaaaaaaaaa
 >AI352454
 HEVESISAQLEEASSTGGFLYAQNSTKRSIKERLMKLLPCSAAKTSSPAIQNSVEDELEMATVRHR
 PEALELLEAQSKFT
 KKELQILYRGFKNVRTFFLTLPSHNSQRSIEK

Fig. 19

P193 (AA349365) DNA (CD:2-127, partial)

TGAAAGTTCTCGAGAAAATGGACCGAACCAAGGATGGGTAGTGACCATTGAAGAGTTCTGGAGG
 CTGTCAAGAGGATGAGAACATCATGAGCTCCATGCAGCTGGTAGAATGTCATCTAGGACACGTCCAAA
 GGAGTGCATGGCACAGCCACCTCCACCCCCAAGAAACCTCCATCCTGCCAGGAGCACCTCCAAGAAA
 CTTTTAAAAAAATAGATTTGCAAAAAGTGAAACAGATTGCTACACACACACACACACACACACAC
 ACACACACACAGCATTATCTGGCTGGCAGAGGGGACAGAGTTCAAGGAGGGCTGAGTCTGGCTAG
 GGGCCGAGTCCAGGAGGCCAGGCCAGCCCTTCCCAGGCCAGCGAGGCGAGGCTGCGCTCTGGTGTAGTGG
 CTGACAGAGCAGGTGGCAGGGCACCCAGCTGGTAGTCAACAGAAAGGGGCTGAGTGGCCCTGAG
 GGAGGGTCCAATCTCCGGTGTGAGGCCAACCTCGTCCCGTCTCCACTCTCTGCCACTACCATGCTT
 CCGCCGCCAGGCTCCCTGGCTCTCCCGTAGCCACTCTCTGCCACTACCATGCTTCTGAAAGGCC
 CTCACCTCAGGACCCAGGGGACAGCTGGGGGGCAGGGGGAGAGGGGTAATGGAGGCCAAGGCT
 GCAGCTTCTGAAATTCTCCCTGGGGTCCCAGGACTCCCTGCTACTCCACTNACCTGGAGAGCTGG
 GTTACCAAGGCCACCCACTGTGGGGCAAGGCTGACTGGTGAGGGGCACTGGGCCCATCTCCCTCCATGG
 CAGGAAGGGGGGATTCAAGTTAGGGATTGGTCGTTGGAGAATCTGAGGGCACTCTGCGAG
 CTCCACAGGGGGTGGAGCCCTCTCCCTGGCCAGCTCTGGTCACTGGGAATGCACTGGGGCTGGCCIG
 ACACACCTCCAGCACAGACTGGTCCCTCAAGGCTCTAGGCTCCGGGAGGAACCTGGTCAAGAC
 TGGCAGGGCAGGGAGGCCAGGGCAGACTAGAGGAGTCTGGGAAGGGGCTGTCCTCTCCCTGTA
 GTGCCCTCCATGGCCAGCAGCTGGCTGAGCCCCCTCTCTGAAGCAGTGTGTCGCCCTCCCTGCC
 GCACAAAAAGCACAGCATTCTAACCTCAGGGCACCCCTAGTGGAGGCCAGCACACTGCTTCT
 CGGAGGGCAGGCCCTCTGCTGGCTGGGCTAGTGGGCCAGTAGGCCCAATATGGTGGCCCTGGGAAGA
 GGCCCTGGGGTCTGCTGTGCTGGGAGTCACTGGGGCCCAAAGGCCAGCCGGCTGACCAACATTCA
 AAAGCACAACCCCTGGGAGACTCTGCTGGGTGTCCTCCCTCATCTGGGAGTGGAGAATGCCAGGCCAAG
 CTGGAGCCAATGGTGGGGCTGAGGGCTGTGGCTGGGTGGTCAAGCAGAAACCCCCAGGAGGAGA
 GATGCTGTCCTGGCTGATTGGGGCTCCTCCAGGAAAGAACCCGGTCCAGGCCCATGGCCCTCCAGG
 AACATTCCACATAATACATTCCATCACAGGCCAGCCAGCTTCACTCAGGGCTGGCCGGGGAGTCCCG
 TGTCGCCCAAGAGGCTAGCCAGGGTGGAGGCCAGGGCTTCAAGGAAAAGGAGTATGGGGAGGGCATG
 GGGGCCCTGGGAGTCAACAGCCCTGGCTCCCTGGAGCTGGCTGCACTGGACGCTGGCTCCAGGCTC
 CAGGCTGACTGGGGCCCTCTGCTTCCAGGAGGGCATCAGGCTTCTCTGCTCAGGGATCTCTCCCTCC
 CTCACCCGCTGCCAGCCCTCCAGCTGGTGTCACTCTGCTCTCAAGGCCAGGCTCAAGGAGGAGCATCA
 CCACCCACCCCTGGGGCTTGGCTGGGGCCAGACTGGCTGCAACAGCCCAACCAGGAGGGGTCTGC
 CTCCACCGCTGGGACACAGACCCGGCCATGTCAGGCTGGCAGAAGCCTCTCCCTGGCACGGCCCTGG
 AGGGTGGTCTGTTCTGACATCCACTAATATTCACTGCTGTATATTAAATAAAACTTGACAAAG
 GAAAAAAAAAAAAAA

P193 PROTEIN (PARTIAL)

ERFFEKMDRNQDGVVIEEFLEACQDENIMSSMQLFENVI

Fig. 20

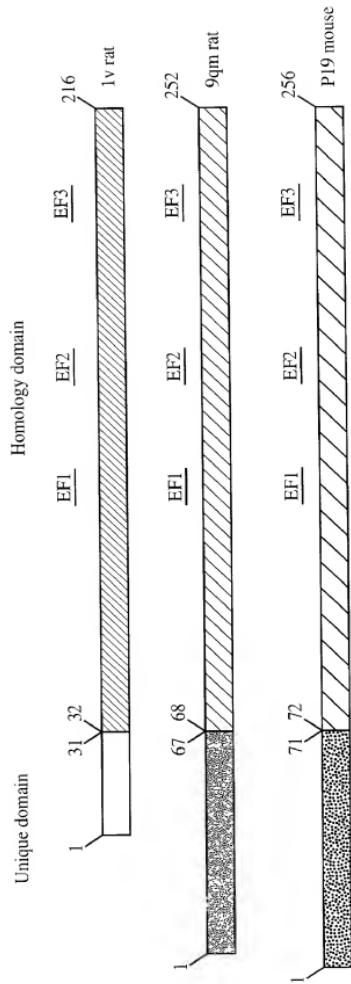


Fig. 21

Human 9q genomic DNA sequences:

A. exon1 sequence (with introns included):

B. Exon 2-11 sequence (with introns included):

Fig. 22

ACTCAGCGNGGGTGGGACAGGAGGCCAANCGGTCCANATTTCANAAAGCATGGCTTNGATGCCTGAGGG
 CGGGCGGAAGGGAGGCAGGCCCTGAGACTGAACCTCTAGCTGGAGGTCTGGGGCGGGGCCAGAACGRAAGTGGCG
 CCTGTAGACTGTCAGTTCTGTTTATTTGCACTGGAAAGAAGTCTTCCCTCCATCACATGAGCC
 ACGTGGTGACTCTCTGGAGGCTGAAGAATTATCCCCCTCCCTGGGACTCTTGGGCCATGGAGGGTGGGGCGGTGA
 ACGGAAAGGGGATTTTGTCCTGCCCCCTCAGGCTGGCCTCTCCTCCAGGAATGTCCACGGGAATTGTCATGAG
 GAGAACCTCAAGCAGATTACTCCAGTCTTCTCTCAAGGAGGTGAGGGACAAAGCCAAGGGAAAGCAGTGTG
 CTCTCTAGCTGAGGGAGGGAGGGATTCTGGAGGAGCTGGAAATGCCAAAGGTATGGGGGATGGGGAGGTCTT
 AGAGGGAGGAAGTCTCTCTGTTGAGGCTGAGCAACTTCTCACAACCTCACCCTGAGACTCCAGAACCTATGCCACTT
 TTCTCTCAATGCCATTGACACCAACCATGATGCGCTGTCAGTTTGGAGGTGAGCTGGCGAGGTGGGCCAGGAA
 GCCTGTTCTGAGGTCAAGGCCAACCCAGAAGAAGTGGGTGAAGAKGCCAGGAC
 ACAGCTCCNTGCTCTCTCCAGGACTTGTGCTGGTGTGGTGAAGGAACTGTAGATGACAGG
 CTTAACTGGCCCTTCAACCTGTATGACCTTAAACAGGAGCGTCATCACCAAGGAGGTGAGGGACACTGAAGGGC
 TGGGGCTGTGCGCTGATGGGGTGGCTGCAKAGGGTGTGGAGGGAAATGACCCACATATGCCAACAGC
 AATGGATCAAGGGAGGTGGAGGCTCTGGAGGAAGGATCTCTTCTCTCTGGCTAACAGGAATGTCATCA
 ATAAGTCATCATGACATGTCAGGCAACTACACTCCACTCTGGGGAGGGCCCAAGGGACACTGGAG
 AGCTTCTCCAGGACTTGTGGAGTGGGTATGGCTGAGGGCCCTGGAGTGAAGGGAAAGGCCAACAGCAGG
 GAACATACCTGACTCTGTGCTCTCTCTGGGATCTGGCTGAGGACTTCTCTGGCTGAGGAC
 TGGACACAAAACAGGATGGTGTGACCATGAGGAATTCTGAGTCTTGTGCAAAAGGATCACGCTCTGGCC
 TACATACCCCTGACCTGGACTCAGGCTGATTAGTAATGCAAGGAAAGCTCTTGGGAAGAATACCCACTTCCC
 ACCTCTCCATTTCACTTCAATTCTCTTGTGGGCTCTGGGCTTACCCCTTACCCCTACGGTCTCTGGCATCT
 CCTCTCTGTGCTTGTGAGTCCTGGCTGTGACTCAAGGTGTCCTCTCATGTCCTGATAAAAGCTCTCT
 TTCTCTCTCAATCTGCTGCTCACATCATGGCCACAGGATGAAGAACATCATGAGGTCCATGCACTCTTGTAC
 AATGTCATCATGCTCTGGGCAAGGG
 CACCCCTCTTCTGCCAGGGTATCTCATCTACGGCTCTGGGGCTGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG
 TAGTCAGACTCTGGAGCTGAAGGGCCAGAGAGTGGCAGAGTGCATCTGGGGGGGGGGGGGGGGGGGGGGGGGGGG
 CTCTCACCCCTCTGGCTGACACCCAGTGTGGAGGCTGGCCCTCTGGTGTGGGGGGGGGGGGGGGGGGGGGGGGGG
 CCCCTACTAGAACACACTAGACAGATCTCTGGCTATGGCTGCTTCCCATGGCTGACCTTCAAAACATTCTC
 CCTAAGACTCCCTCTAGAGAGAACATGCTCATTCTGGCACTGGCTGCTGGCTTCTCAGACCACCATGGAGAGCCCTG
 TGGGAGGG
 GAGAATAGAAGGGCTGAGGAGATTGATGTCAGGCACTTACAGGTTATAGCTTCAAGTTCACAGGCTGTCAC
 CACAGGCCATAAAATAAGTTCCAGGCTTGCAGAAGACCTGTCTCTTAGAAAATGCCAACAGAAATTTCAC
 ACCCTCTCTGGTCACTGGAGACCTGGGGCAAGATATGCTGCTCATCTGGCTTCTCTCTCTCTCTCTCT
 TGCACTGTTGTTGGTGTGGTGTGG
 CACCCCTCTTGCTTATGTCCTCTGGGCTATGACTTGTGAGTTTTGGTCTCATGTCCTATAGACTTGGG
 ACCCTCTGAACTTGGGGCCCTATCACTCAGGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
 GCATCTGACCCACTGTGGGGCTTCACTCAAGAATCTTCAACCTGGGCTCTCCCAACCCCCAGATAACC
 TCCTCAGKTCCCTAGGGCTCTTCTYGTGACTCACTACCCAGAGATGCCCTTAGCACACACTAGAGGGCAGGG
 ACCATAGGACCCAGGGTCAACCCCAATTGTCAGCACCCCAAGGCCATGGCCACCCCTTAGCACACACTGCTGCTCCA
 TTAGCTTACCCCTCCAGTGTGGCAGAACTGAGGGGAGGCCCAAGGAGGCCCTTCCCATCAGAACACTGTT
 GACTGCTTGTGATTTGGGCTCTCTGCTCTTGTGACTTATATTTGTAAGAAGAATATACAGATC:TAATAAAACAAATGGC
 TATGACACGGCTGGGGCTCTCTGCTCTTGTGACTTATATTTGTAAGAAGAATATACAGATC:TAATAAAACAAATGGC
 GCCTTTAGATCCCAAAGAAGTGGCTTCTTTCATAGTTGGCCATACCTTGGCATGAGACTGAGACACAGGCTC
 TGGATGGTGGAAACCCACCAACCTCAGGCCCTACATGAATCTCCCTCCACACGCCCTGAGGAGGAGACAAGGA
 AGGAAGGACAGGACACTGATGTCCTGGCAAGGACTGTGCAACCAAGCTGTTTTAGCTGACATTTCAAGTTGAAT
 CACAGATTCTAATTCAAGACTTTAGTTAATCTCAAAAGTGTCTTCTTTGAGGGGCTCTTAAAGTCTT
 TTTTTTTTTTTTTTT

Fig. 22 Continued

>monkey KChIP4 cds = 265

gtcgacccacggcgtccgggtgcgtggaggccccggggagcccccggccaggccaaatgcaggatcagcatgagaggctgg
 actttagtccagggtctgttcaccccccggggacccgggtttgcagggtgcactgcggaggactgtcactttttcc
 cccttgcgaatctttgttcaacgcgtacgttgcataattactccactccaaagggtctggggc
 tgggatgtctgcgcagctcagaggATGTTGACTCTGGAGTGGAGTCGAAGGACTGCAAAACAGTGGGTA
 TTGTGTGAT
 TATATGTCATCTCTGAAGCTGCTCATTTGCTGGGACTGATTGATTTTCCGAAGACAGCGT
 GGAAGATGAACTGGAGA
 TGGCCACTGTCAGGCATGCCCTGAGGCCCTGAGCTTCTGGAGCCCAGAGCAAATTAC
 AAGAAAGAGCTTCAGATC
 CTTAACAGAGGTTAAAGAACGAATGCCCACTGGTGTGTTAATGAAGAACCTCAAAGA
 GATTTACTGCCAGTTCTT
 TCCACAGGGAGACTCTAACACATATGCACATTCTGTCATGGCTTGTACGGACACA
 ATGGAGCTGTGAGTTCG
 AGGATTTCAAAAGGTCTTCCATTGCTCGGGGACAGTACAAGAAAACCTCAATTGG
 GCATTTAAATCTGTATGAT
 ATAAATAAAAGATGGCTACACTAACAGGAAATGCTGATAATGAAAGCAATATACG
 ACATGATGGTAAATGTAC
 ATATCCCTGTCCTCAAAGAAGATGCACCCAGACAAACAGTCGAACACATTTCAGAAAATGG
 ACAAAAAAAAGATGGGG
 TTGTTACCATAGATGAGTCTATTGAAAGCTGCCAAAAGATGAAAACATAATGCCCTCATG
 CAGCTCTTAAATGTC
 ATTAAActgtcaactagacttgcataatccaaacagacaatgtgaactattctaccaccccttaaagtggagttaccactt
 ttgcataatggctcgttgcactgttgcataatggccaaacttgcataatggccaaatgttgcataatggccaaatgttgcataat
 ttgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 ttgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 tcgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 actgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 aaacaataagattactaataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 ttatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 agcatttaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 gttttccatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 aggatattatccatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 cccctgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 aacaacaaacaggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 gaaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 aatcatctcagccacaactgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 gaccaagggatcagaaggaggaaatttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 gatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 tggccatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataatggccaaatgttgcataat
 aaaaaaaaaaaaaaaa

>monkey KChIP4

MLTLEWESEGLQTVGIVVIICASLKLHLLGLIDFSEDSVEDELEMATVRHRPEALELLEAQSKFT
 KKELQIYLRYGFKNE
 CPSGVVNEETFKEIYSQFFFQGDSTTYAHFLNADFDTDHNGAVSFEDFIKGLSILLRGTVQEKLNW
 AFMLYDINKDGYIT
 KEEMLDIMKAIYDMMGKCTYPVLKEDAPRQHVETFFQKMDKNKDGVVTIDEFIESCQKDENIM
 RSMQLFENVI

Fig. 23

```
>monkey KChIP4 C terminal splice variant
MLTLEWESEGLQTVGIVVIICASLKLHLLGLIDFSESDSVEDELEMATVRHRPEALELLQAQSKFT
KKEELQYLRYFKNE
CPGSVVMNTEFFKEIYQSFFPQGDSTTYAHFLNFAFDTDHNGAVSFEDFIFGLSILLRGTVQEKLNW
AFNLYDLDNKDGYT
KEEMPLVYIYDMMGKCTYPVLKEDAPRQHVETFFQAVFHCIIKWKFKTASNKTRMFTDICK
GGSYLLSSCIC
```

Fig. 24

KChIP1_1v		MCAAGCTT	SSEQTQ	--RKE
KChIP2_9q1	MRGGQRKESLSDSRLDGSYDQUTGPPGT	TKAKLAKORFLVPLCCGPQALPSVSETLAA		
KChIP3_p19	-MQPAKEVTKAS	DGSLLGDLGH	TPSKKEGLKWQRPLRSQALMRCCLVKWI	
KChIP4_352	--MLTLEWESEGGLQTVGVLVILICAS	LKLHLHLGLIDFSE		
KChIP4_231	--MLTLEWESEGGLQTVGVLVILICAS	LKLHLHLGLIDFSE		
hsncspara	--HEVEISIAQLEEEASSTGFLYAQN	-STKRSIKERMLALIICS		
<hr/>				
KChIP1_1v		-SKDKIEDELEMATVCHRPEGLEQLEAQTNKRELQLVLYRGFKNECPS		
KChIP2_9q1	PASLRPHPRRLDPDVDEFELSTVCHRPEGLEQLOEOTKETRKRELQLVLYRGFKNECPS			
KChIP3_p19	LSSTAPQ	--GSDSSDSELELSTVRHQPEGLDQLOQTKFTKKELQSLYRGFKNECPS		
KChIP4_352		-DSVDEDELEMATVHRHPEAELLEQASQSKETKKELQTLYRGFKNECPS		
KChIP4_231		-DSVDEDELEMATVHRHPEAELLEQASQSKETKKELQTLYRGFKNECPS		
hsncspara	-AAKTSSP	--AIQNSVEDELEMATVHRHPEAELLEQASQSKETKKELQTLYRGFKNECPS		
<hr/>				
KChIP1_1v	GIVVNEETPKQTYAOFQFPHGASTAYAHLFNAFBITQGTSVKFEDFVTLASILLRGTVHE			
KChIP2_9q1	GIVVNEETPKQTYAOFQFPGDSSTYAHLFNAFDINHDGSVSFEDETVAGLSVILLRGTVHE			
KChIP3_p19	GIVDDETPFKLTYAOFQFPGDATTYAHLFNAFDNGAIIHFEDPVGLESILLRGTVHE			
KChIP4_352	GIVVNEETPKETTYAOFQFPGDSTTYAHLFNAFDTHNGAVSFEDFIKGLSILLRGTVHE			
KChIP4_231	GIVVNEETPKETTYAOFQFPGDSTTYAHLFNAFDTHNGAVSFEDFIKGLSILLRGTVHE			
hsncspara	FETLPLSHNSQRSIEK			
<hr/>				
KChIP1_1v	LRMTFNLYDINKDGYIINKEMMDLIVKATVDMMGKYTTPVWLKEDTPTROHVDFVFFQKMD			
KChIP2_9q1	LNWAFNLYDINKDGYIINKEMMDLIMKSIVDMMGNYTTPLREEPAREHVESFFQKMD			
KChIP3_p19	LKWAFLNLYDINKDGYIINKEMMDLIMKSIVDMMGNYTTPLREDPAEHVERFFQKMD			
KChIP4_352	LNWAFNLYDINKDGYIINKEMMDLIMKAIVDMMGCTTYPVWLKEDTPTROHVDFVFFQKMD			
KChIP4_231	LNWAFNLYDINKDGYIINKEMMDLIMKAIVDMMGCTTYPVWLKEDTPTROHVDFVFFQKMD			
hsncspara				
<hr/>				
KChIP1_1v	--KKNKDGVITLDEFLESCQEDDNIMRSLOLQFNVM			
KChIP2_9q1	RNKDGVTVIEEFLSCQDENIMRSMQLEPDNV			
KChIP3_p19	--RNDQGVTVIEEFLACOKDENIMMSMOLFENV			
KChIP4_352	--KKNKDGVITLDEFLESCQDENIMRSMQLEPDNV			
KChIP4_231	IKWKFKTASNKTRMTDICKGSGYUSSSI			
hsncspara				

Fig. 25

Rat 33b07 protein

MNNGVEGNNELPLANTSTSALVPEDLDLKQDQPLSEETDTVREMEAAGEAGGASPDEHCDPQLCLRVAENGCAAAG
 EGLEDGLSSSKCGDAPLASVAANDSNKNGCQLAGPLSPAKPTLEASGAVGGLGSQMMPGPKKTKVMTKGAI SATTGKEG
 EAAGAAMQEKKKGKVQEKKKAAGGGKDETTRPRAPKINNCMDSLEAIIDQELSNVNAQADRAFLQLERKFGRMRRLHMQRRSFII
 QNIPGFVWTTAFRNHPQLSPMISQDDEMMRYMINLVEEELKHPRAZCKFKFIFQSNPYFRNEGLVKEYERRSSGRVVSL
 SFIRWHRGQEPQAHIIHRNREGNTIIPSFFNWFSDHSLLEFDRIAEIICKGELWSNLQYYLMGDGPRRGVRVPPRQPVEPSR
 SFRFQSG.

Rat 33b07 DNA (coding: 85-1308)

GGTGGAGCTAACGCACTACTCGGGTCTGCCCTCGCTTCGAGAGAACAGGAAAGCTCTCGCAGGGCTGTCACTGC
 CAAAATGAAACGGCGTGGAAAGGAACACGAGCTCCCTCTCGTAAACACTCGACCTCCGCCCCCTGTCAGGGAGATCTGG
 ATCTGAAGCAAGACCAAGCCGCTCAGGGAGAAACTGACACGGGGAGATGGAGGCTCGCAGCTGAGGGCTGAGCAG
 GGAGGCGCCGAGGCGATTGGAGACCTGGCACCCCCGACTCTGCTCCGAGTGGCTGAGAATGGCTGAGCTGCGCAGC
 GGGAGGAGGGCTGGAGGATGGTCTGCTTCATCAAAGGTGAGGCGACCCCTGGCGCTGTGGCAAGCCAACGACAGCA
 ATAAAAATGGCTGTCAAGCTTCAGGGCGCTCAGGCCCTCTAAAGCaaaaACTCTGGAAAGCCAGTGCTGGCTGAGTGGCTG
 GGGTGGAGCATGGTGGAGGGCCGPAAGAAGAACAGGTAATGACTAACAGGGCAGCCTCTGGCAACTCTGGCAACTACAGGCA
 AGGAGAACGAGGGGGCAAGTGGAGGAAAGGGGGTGGAGAAGAAGAAAAGGGAGCTGGAGGAGGGAAAGCAGAGA
 CTCGTCCTAGACCCCTAAAGATCAATAACTGATGGACTCCCTGGAGGACATCGATCAAGAGCTGTCAAATGAAATGCG
 CAAGCTGAGAGGGCCCTTCCAGCTGGAAACGAAATTGGGGGATGGAGAAGGCTCCACAGCCGGCAGGTTTCT
 CATCCAAACATCCAGGTTCTGGGTCAAGCGTTGGAACACCCGCAACTGTACCGATGATCAGGGCAAGATG
 AAGACATGATGAGGTACATGATCAATTAGGGTGGAGGCTTAAGCACCAGGGTGCAAAATTAAAGTTCTAC
 TTCCAAAGCAACCCCTACTCCGAATGAGGGCTGGTCAAAGAGTACAGAGCAGCAGATCCTCAGGTGAGTGGTGTGCT
 CTCTACGGAATCCGCTGGACCGGGGTCAGAACCCCAGGGCATATCCACAGGAATAGAGGGGGAAACAGGATTC
 GTTTCTTCATTTGGTCTCAGACCCAGCCTCTAGAACATGGCTCAGAACATAGCTGAATATTCAAAAGGGAGCTTGGTCC
 AATCCCTCAAAATACTACCTGATGGGGGATGGCCACGGAGGGAGTTGAGTCCACCAAGGCAGCAGTGGAGAGTCC
 CAGGTCTTCAGGTTCCAGTCTGGCTTAAGCTCTGCCCTCTGAGGAAGCTCTAACAGAAGAGTCTTAAACCCCTTCTCAGC
 TTGGCTAGGAGCATCAGCCCTCTGCTGTTCTCTCTGGTGTCTGGTTCTTCTAAGTCTGGGAGTGGT
 TCAAGGTGTGGCTTCAAGGTTCTCTCTCTGGCAATCAGATGATCTGGCATAGTTAAGTGGT
 GTCAAGTGGCCTCAAAACTGCTTCTATGCCAAGCTCACGTGCTGTAGTTGTACTGCTTCTTGCATGGCTGGTCT
 GTCTGTGATCTCTAGGTTTTCTTTCTTTAAAGTGGTCTCTATCAAAGAAAAGCTTGACATTCCTTACCAA
 GAACTAGCCAGATTCTACACTGTGTTCCGATATCTGACTGTGAAGAAACTGTGAGTTTCGCCACTGCAAGATGGAC
 TGATCTCCAACTCAGGCACTCAGCCAAACAGGACATTCCAAAGCTGTCACCAACTGATCTGCTTCTCTGGGCCCTTG
 CCATTTCACCTGCTTTTATCTATAGAATGAGCAGGGCTGGTAGGTGACTACTAGGTAAAGACTGAAGTATTAGGTGAG
 GAGTGTGTTCTGTGACCACTTGTCTTGTACCAATGATGATCAGCTTGGATCAGCTACTGACTGTCGATATTTC
 TAACCCCCAACACAAAAAAAAAAAAAAAAAAAAAAAAAAAAAA

Fig. 26

Human 33b7 (106d) protein
MSGLGDGNKLPLAQTTGGLAAPDHASGPDPDLCQCGLREETEATQVMANTGGOSLETVAEAGGAQSQDPVDCGPAVLRRVPVAGS
RRAAATGCAQDEPAPSTKLGEEAASAAEADSSQKNGCQLGEPPGPGAPQKALEACGAGGLGSQMIPGKKAKEVTTTKRRAIS
AAVEKEGEAGAMVQFVWTTTVAEKKVAVGGKEVTRPRAKINNCNMSDLSLEIQLDSNNVNAQDRAFLQLERGRGMRLRLL
QRSSFTIQQNIPGFVWTTAIFRNQPLQSMGQDDEMLRYMLNEVLEELKHPRAFGCKFFIQPQGNGRNEGLVKEYERRSS
GRVYSSLSLTIRHWRQDQPAHIIHRNREGNTIPSFFNWFSDHSLEFDRIAEIKGELEWPWNPLQYYLMGEGPGRGIRGPPF
OPVSEASRSFFOSG

Fig. 27

Rat 1p protein (partial)

LKGARPRVNVSTCSDFNHSALHIAASNLCLGAAKCLLEHGANPALRNRKQGVPAEVVPDPMDMSLDKAEEAALVAKELRT
LLEEAAPLSCLTPKVTLPNYDNVPGNLM SALGLRLGDRVLLDGQKTGTLCFCGTTEFASGQWVGVELDEPEGKNDGSVG
GVRYFICPPKQGLFAVSVKSKAVDAPPSSVTPTPRMDSRVTGKGRREHKGKKSPSSPLGSLIQREGAKAEVGD
QVLVAGQNRDCAFLWEDEPLCSRLLVWVH

Rat 1p DNA (partial, coding:1-804)

CTGAAAGGGCGAGGCCAAGGGTGTGAACCTCACCTGCAGTGACTTCACCATGGCTCAGCTGACATCGCTGCC
GAATTCTGCTCTGGGGCCGCCAATTTCTAGGGACATGGTCAACCCAGCCTGAGGAATCGAAAAGGACAGGTAC
CAGGGAAAGTGTCCAGACCCATGGACATGGCTTGTACAAGGCAAGGGCAGCCCTGGTGGCCAAAAGGAATTGCGGACG
CTGCTAGAGAGGTGTGCACTGCTCTGCACCCCTCTCAAAGTCACACTACCCAACATGACAAACGCTCCAGGGCAATCT
CATGCTCAGCCGCTGGGCTGGCTTAAGGACGCCAGTGCTCTGGCATGGCCAGAAGACGGGACAGCTGGTCTCG
GGGACCCAGTTGCGCACTGGCCAGTGGGGCTGGGGCTGGAGCTAGATGAACCGGAAAGGCAAGAACGCCAGCCTGG
GGTGTCCGGTACTCTCCTCCAAAGCAGCTCTTGTGATCTGTCCAGGTCTCAAGGCTGGATGACCC
CCCCCTCATCTGTTACCTCCACGCCCCGCACTCCCGATGGACTCTCCCTGTAAACGGCAAAAGCCGGGAGAACACA
AAGGGAAAGAAGAACTCCCACTCTCCCATCTCTGGCAGCTGGCAGCTGGCAGGGCAAAAGCTGGCAAGTGGAGAC
CAAGTCTCTGGCAGGCCAACAGGATTGCTTCTATGGGAAGACAGACTTTGCTCAGGTACTCTGGATGGCA
TTGAACCTGGACCCAGGCCAACGGCAACGATGACCGCTCTGTGTTGGTGTCCGGTACTTTACCTGTGCCCGAGGCACGGG
GTCTTGACCCAGCATCTGCTATCCAGGATTTGGTGGATCAACTGATCCCCCTGGAGACAGTGTGGACCAAAAAGT
GCATACAGTGAACATGACAGCCCACAGCCTTCACAAACGTCGGACCCCAAAAGGACATTGCACTCAGAGAACTCTA
TCTCCAAAGTGTACTCTGCTGCTGGTTCTCTGGATGCTGAGGGCAGGAGATGCACTTAGAGACCTGGATACCTGACA
CAGAGACAGTCCCTCTAGCATCTCTGCACACAAGGAGACCCAGTCACCTAAAGATAGAGATTCCTCAGTCACCC
CAGAAATGAGAACCCCGTTAGGCCAGCCCTCGATTACTGGGCTTCATTAAACGATCTCCAGGACTCCCCAAAT
ACAGACCTGATGTTACCCAAAAGGATCTCTGGTAGCACCCTCAGGCTAGTCCCTGTCCCCCTACCCAGCAGGAG
TTTCCCCCAATAAACATTCTCCACATCCCCAGGATGCTGACCCCTCTCACGACAGGAGCTTGTAGTTACAGTGG
ATTAGAGTCCCATGAATGAAGACCCCCCCCCACCCGGTTCTCTTAAGCATAGGTCTACCTCCAGAAATGCCAGCACA
TCACACTCCCCATGTAACATCAGTCTCTCAAAATGGCTGGGTGAGGTACTAGAAAGACCTTAACTCTCTCTCTCA
GAGATGCCCTCATTCAACTAGTCCCTGTTGACCCCTGACAAAGACACTTAATTAACCGGCCACTCACCTCA
CAAACACCAAAATCTCTGGAACATGAATTAACAGGACAGCAGTCTCTCTGCCCTGTGACCCCTTGAGAAACCC
TGCCTGTATGAAGGCCACCCACATGGCCCAAGCTGCTCTGCGCAAGGCTCCAGAAAATTCTCTTTTAA
GTAAATACTCCCCCCCCCTTGGGGGATCCCCAAATTGGAGACCCCATCTAGAACACTGGGGAGTCCAAATTCCAGAG
AGATAATAATTATAATACCTCCAAATCCCCATGCTTCAAGGCTTACCAACTCTGAGAAAGCCCAAATTCTAA
CCAGGACTTCCCCCTACCAAGTCAGAACTCTCAAATCCCCAGGGAACTCCAAACTTAAGATAACCAATCCAAACCC
AGGAAATCCCCAAACACAGTCTCTAGGACCCGGAGGAAGGAACTGTGGCCAGGAAACATCCAGGCTCTCAGGCA
TCTCAAACTGTACTCCCAGGACCCAGGAGACCCAAACAGAAAGCTTGGGAACAAGGATAGGACTCTAAACCC
TTAGTCCATGGATCTTAAATTCTCCAAACTCTCATGGGCCCCACCTCTCAAGGGAAACCCCAAGATCCAAATCTC
TGATAACTAATATGTGCAAGGGCCCCAGGGCTTAACAGGACCCAAATCATGGAGTCCCTACTCTCAATCTACCTTCTGG
CACAGGTCAAGACACTAAATCTGAGTCATGGCCCCAAAGGACTTCAGCAGCTGGCCAGACTAACAGCTGAGGG
GAACCTGAGGGCCCCGTGGTCCAGAGCAGACCTGGGCCCCGACCCAAAGGACAGCTCACGACTGCCCTTACTGCA
TGTCTCTAAACTCAGCATGACTCTGTCTCTCAATAAGAGCTTCTATGGCAAAAAAAAAAAAAAA

AAA

Fig. 28

Rat 7s Protein (partial)

ADSTSRWAELREISGRLAEMPADSGYPAYL GARLASFYERAGR V KCLGNPEREGSVSIVGAVSPPGDFSDPVT SATLG
 IVQVFVGLDKKLAQRKHFPSVNLLISYSKYMRALDEYYDKHETEFPRLRTAKEELQEEEDLAEIVQLVGKASLAETDKI
 TLEVAKLIKDDFLQQNQYTPYDRFCPFYKTVGMLSNMISFYDMARRAVETTAQSDNKITWSIIREHMGEILYKLSSMKFK
 DPVKDGEAKIKADYAQLLEDQNAFRSLED

Rat 7s DNA (partial, coding: 1-813)

GCTGACTCTACCTCTAGATGGCTGAGGCCCTCGAGAAATCTCTGGTCGCTTAGCTGAATGCTGCAGATAGTGGATA
 CCCCCTGCATACCTTGGTGCCTGCACTGGCTTCTCTATGAGCAGGAGCAGGTGAATGCTTGGAAACCCCTGAGAGAG
 AAGGGAGTGTCACTGAGGACAGTCTCCACCTGGTGGTGAATTTCCTGATCCAGTCACATCTGCTACTCTGGGT
 ATTGTTCAGGTGTTCTGGGCTTGGAAGAAGCTGAGCTCAGGCAAGCAGTCTCCGTCGCTCAACTGGTCATTAGCTA
 CAGCAAGTGAAGGGCGCTGGCGAGTATGAGCAACACTCAGAGTCTGGCCTCTGGAGAACCAAAGTCAAGG
 AGATCTGAGGAAGGAGGGAGTCTGGCGAAATCTGAGCTGGCTGGGAAAGGGCTTTAGCAGAGACAGATAAATC
 ACCCTGGAGGTAGCAAACCTTACAAGATGACTCTCACAAACAAATGGGTACACTCCTTATGACAGGTCTGTCATT
 CTATAAGACGGCTGGGGCTGTCGCAACATGATTCTATCTGATGATGCTGGCGGGGGCTGAGGACCCGCCCCAGA
 GTGACAAAGTAAAGACATGGTCATTATCGCTGAGCACATGGGGAGATCTATAAAACTTCTCCATGAATTAAG
 GATCAGTGAAGGGCGGCAAGATCAAGGGCAACTACCACAGCTCTGAGATATGCAAGAACGATTCGAG
 CCTGGAAGATTAGAACTGTGACTTCTCTCTTCCAGCTCATATGTTAATTTCTGATATACTTCATCC
 ACCCTGGCTTCCATATTGTGAGGAGACTGTGCTCTGGCTGCTCTGCTCATTTCTGTTCTGGTAGGTC
 TTATAAAACACACATTCCTGTCTCGGTGTAAGGAGCTCTGACCTTGTGAGTGTGATGTTAGTCATATG
 ATACACAGTGTAAACATCACATGTAACATATACGTTCTGTAACCTGTGATGTAAGGTGACTACCCCTCC
 AGTAAACTGTAAACAGGACTACTGTGATGTCATTTGGGGATGGAAGGCCAGTCTCCATACCGGACAGGTACATAA
 GGAAACTAGACCACTTGTGACTTGTGAGTAACCTTTCAGGAACTTTCAGGAGTAACTTAAACAAAGATT
 AATTTCCCAATTATTGTTAGCTTCCAGTATCAATCAGGACTCTGGCTGCTGCTCATTTCTGAGGACTT
 CAGAGCTTGTCAAGGCTGAACGTAATAGATAAATCAGTCTCTGAAAGTGTGAAGTAAAAGAGAGCTAGGTGTC
 GACTTTAAATGACATGCTCTGTTAAAGCATTTTATTCAGAGGATTTAATATCAAGGACTTTATATACAT
 TACTAGGAAATCTTTTAACTTAAATTTAAATCAGTAAATTTGACATCATAGCATTCTTCTTAA
 GTCAAGATGAGCTCAGAGTGGGGAGGTGTTAGAATACCAAGGACACGCACTGGCTGAGGAGTGTGGCG
 GGGGCCAGAGCGGCATTGTTTACAGGGTACGTGTTGGCTGTGTTGCTGTGACACTCTGAAACAGCAAGCT
 TACCAACAGCGTAACGACAAGTATTATTAACTTCTACTGGCTCAGAAAGCTCTCAAGTACCTGGCTCTGAAGCTTCT
 CTGTTAATAGAGGAGAGGAGCTTCAATTAACTTGTGACAAACAAAAGAAAAAGATGCAATTGTTGCTTC
 TGTTTGGTGTGTTAAATATAATTCCATATTGACATAACGAGGCTGCTCTGAGAGCTTGGAGATGTCCTCT
 TCACTCTCCGGGGTGTATAATGCTGGGGCATCTCTCAGGAGGGAAAGGGGATTGAACATGGCTAACACTCTCAA
 GTACACAAAGCGTAACGACAAGTATTATTAACTTGTGCTGTTAAATTAGTGTGCAATTCTTATGTT
 CTTTGGGTAGACATGATACACTTCAGATTTAATGTTAACTCTGCTAGTGTGATGCTACACGATAGATGCTATT
 CAAGAAGGATATTCTTCACATAACAAATTAAAACATTAAATCAGATATGAGGATTATGCAATGACTTTGAGAGGTG
 ATTAACGGTGTGCTGCTTAATCAGTTGCTTCACATGCTTGGCTTGAAGAGGCCCTGACTAGTGGAGATGAGAAAGATT
 TCAAAACCTGTCTGCTCACCTACAGCACCTAGGGCTGTGATCAGAATGAATGATGCCAAAGAAACTACTTGACCAAG
 TGTGTTTGTGTCCTGGGATTGAGATGTCGGTTCTCTCCCTCTGAGACTGTGATGTTAGTGTGAGAAGTTACA
 GAAACAAACGCTCAGATTTCACGGTAACCTTCCCTGCCCCACACTGTAGAGTTCTGAGATTGTCATGATGCTCT
 TTGCTAAGGATGTTAAATATAGCAGCTTAAAGGATTATGCAAGTCTCTATTTTATTGTGCTGCTGCTGCT
 AGTCAGCGGGTAAACAGGTTATGTTTCAATTGTTTCAAGTGTAAATCTCATACCTATGCCCTTGGAAAGCTTCT
 TGAACAAATGAATAGAAGGCTATAAAATTGCTCTTATCTTAAAGTTCACTATCTTATGTTAAGAGTAATGTT
 AATTATTAAATCTATGAAAATAAAAGTGGATTAAATTAAGAGATC

Fig. 29

Rat 29x protein

ARLPAPEEARQQLLSGPPEGSSARVPVPGVASRRQPRGGKPPSGDGLESGPSPRPLLHARGEAGLHRQSGRVPHTGTAY
 FADEPTEAQAPGGFCVSPSLLGVRWPACATRTPGSPLSPPSAQPRTLWPTPAGPSSRMVARQVAADNAISPASEPRR
 RPEPSSSSSSSPAAPRPRPCPVVAPAFGDTHFRTFRSHSDYRIRTRTSALLDAGFYWGPLSVHGAHERLRAEPVG
 FLVRDSRQRNCFFALSVKMASGPTSIRVHFQAGRFLHDGSRETDFCLFELLEHYVAAPRRLMLGAPLQRVRVPLQELCRQ
 RIVAAVGRENLRALIPLNPVLRDYLSSPFQI

Rat 29x DNA (coding: 433-1071)

GCACGGCTCCGGCCCCGGAGCATGGCGGACAGCAGCCCCCTCCCTCGGGCCCTGAGCCCGGATCGTCGCCCGGGTTCC
 AGTCCCCGCGTGGCCACTAGGCAGCGAGCCGAGGGCAAGCCACCCAGGGGAGCGGCTGGAGTCGGCCCTCTC
 CACGGCCCTCTTCACGCCGGCGGGAGGCCAGGGCTCACGCCAGTCTGAAAGGGTCCACATACAGGAACGGCTAC
 TTGGCAGATGAGCCCACGGCTCAGGCTCCGGGGGATTCTGCTGTACCCCTGCTCCGGGCTGGCCG
 CTGTGCCACCCGGACGCCGGTCACTGCTCTGTCCTCCCATCAGGCCAGCCGGGACGCTATGCCAACCCCTCAG
 CTGGCCCTCTCAGTAGGTTGAGCTGGACGACTAACAGGTTGCCAGACAATGCGATCTCCCGGATCAGAGCCGAGGG
 CGGCCAGAGCCATCTCGTCTCGTCTCGTCTCGCAGCCGGCGCTCCGGGCTGCCGGTGGCTCCGG
 CCCGGCTCCGGCCGACACTCACTCCGACCTCCGCTCCACTCTGATTACCGCGCATACTCGGCGACCAGCGCTCC
 TGGACGCTGCGGCTTCTACTGGGACCCCTGAGCTGAGATGGGGCCACGAAACGGCTGCGTGCGAGCCCGTGGCACC
 TTCTTGTCGCGACAGTCGGCAGCGGAACTGCGCTTCAGCGTGAAGATGGCTTCGGGCCCCAGCAGCATTG
 TGTGCACTTCCAGGCCGGCGTTCACCTGGACGGCAGGCCGAGACCTTGCACCTGGCTTCAGCTGCTGGAGCAGT
 ACCTGGCCGCCGCCGCGCATGTTGGGGCCCACTTGCGCAGGCCGCGTGCAGCCGCTGCAAGGAGCTGTGCGCCAG
 CGCAGTCGTCGGCCCGCTGGCTGGAGAACCTGGCAGCATTCCCTTAACCCGGTACTCCGTGACATCTGAGTTCC
 CCCCTTCAGATCTGACCCGGCTGCCCGCAGCATTAAGTGGAGGCCCTTATATTCTTATTAAATT
 ATTATTTTTCTGGAACCACTGGAGGCCCTCCCGCTAGTCGGAGGGTGGAGGGTGGAGATGCCCTCCACT
 TCTGGCTGGAGACCTTATCCGCTCTGGGGGCGCTCCCTGGTGTCCCTCCGGTCCCTGGTGTAGCAGCT
 TGTTGCTGGGGCAGGACCTGAACTCCACGGCTACCTCTCCAGTATTACATGTTCCAGTATCTTGCACAAACCAGGG
 TGGGGGAGGGTCTCTGGCTTCATTTTCTGCTGTGCAAGATATTCTTATTATTTACATCCAGTTAGATAAAA
 CTTTATTATGAAAGTTTTTTTTAAAGAAAAAAAAAAAAAA

Fig. 30

Rat 25r DNA (coding 130-

GGCACGGCTCCGGCCCCGGAGCATGCGCGACAGCAGCCCCGGAAACCCCCAGCCGCGGCCCGGTCCCGCCGCA
 GCAGCCCCGGAGCCTATGCCAACCCCTCCAGCTGGCCCCCTCAGTAGGATGGTAGCACGTAACCAAGTGGCAGCCGACA
 ATGCGATCTCCCGGCATAGAGCCCCGACGGCGGCCAGAGCAGCATCTCTCGTCCTCGTCTCCGCCGGCGCCCCCG
 GCGCGTCGGCCGGCTGGCCCGTGGTCCGGSCCCGGCTCCGGCGACACTCACCTCCGACCTTCCGCTCCACTCTGA
 TTACCGGGCATCACCGGACAGCGCTCTCTGGACGCCCTGCGGCTTCTACTGGGGACCCCTGAGCGTGCATGGGGGC
 ACGAACGGCTGCGTGCGGGAGCCCCGTTGGCACCTTCTGGTGCAGCAGTCGCCAGCGGAAC TGCTCTCGCGTCAGC
 GTGAAGATGGCTTCGGGCCCCACGAGCATTCGTGCACTTCAGGGCGGGCCCTTCCACCTGGACGGCAGCCGGAGAC
 CTTCGACTGCTCTTCGAGCTGCTGGAGCACTACGTGGCGGCCGCGCCGATGTGGGGCCCACTGCCGCCAGCGCC
 GCGTGCGGCGCTGCAAGAGCTGTGCGCACCGCATCGTGGCGCCGCTGGTGCAGAAGACCTGGCACGCATCCCTTT
 AACCCGGTACTCCGTGACTACCTGAGTTCTCCCTTCAGATCTGACCCGCTGCCGCCGAGCATTAAGTGG
 GAGGCCCTATTATTTCTATTATTAATTATTATTATTCTGGAACCACGTGGAGGCCCTCCCGCTAGGTGGAG
 GAGTGGGTGTGGAGGTGAGATGCCCTCCACTCTGGCTGGAGACCTTATCCGCCCTCTGGGGGGCCCTCCCTCTGGT
 GCTCCCTCCGGTCCCGCTGGTTGAGCAGCTGTGCTGGGGCCAGGACCTGAACCTCACGCCACTCTCCATGTTA
 CATGTTCCAGTATCTTGACAAACCAACGGGTGGGGAGGGTCTCTGCTTCAATTCTGCTGAGAATATTCTAT
 TTTATTTTACATCCAGTTAGATAATAAACTTTATGAAAGTTTTTTAAAAAAAAAAAAAAA

Fig. 31

Rat 5p protein

MPSQMEHAMETMMLTFHRFAGEKNYLTKEQLRVLMERFPGFLENQKDPLAVDKIMKLDQCRDGKVGFQSFLSLVAGL
IACNDYFVVHMKQQK

Rat 5p DNA (coding: 52-339)

CTTCCAAAAGACTGCAGGCCCTCAGGGCCCAGGTTCAACAGATTCTCAAATGCCATCCAAATGGAGCATGCCATGGAA
AACCATGATGCTTACATTTCACAGGTTGGCAGGGAAAAAAACTTGTACAANAAAGGAGGACTGAGAGTCTCATGGAA
GGGAGTCTCCCTGGGGTTTGGAAACATAAAGGACCTCTCGGGTGGCAACAAAATAAGGAACAGCTGGACACCTGGCA
ATGTTGGAAAAGTGGCTTCAAGACGTTCTACTAAGTGGCGGGCTCATCATTGCAATGACTTATTGTGAGTACA
CATGAAGCAGAAAAGTAGGCCAATGGAGGCCCTGGTACCCCACCTTGATGGCTCTCCCATGGGGTCAACTGAGGA
ATCTGGCCCCATCTCTCTGGTGCAGGAGATCAGGGACCTTGTGAAATGTGCAAAATAACATCCTAACCTGCAACAGCA
GAGAAAAGAAAGTAAATCTAACATGACAGGAGGACTTGTGAGTTTATATGGTTGATCGGGTTCCTAACAAAGGAAAG
CTTPTTTTTTAAAGTTCCGAAAAAaaaaaaaaaaaaaaa

Fig. 32

0957057957950

Rat 7q protein

MAYAYLFKYIIIGDTGVGKSCLLLQFTDKRFQPVHDLTIGVEFGARMITIDGKQIKLQIWDTAGQESFRSITRSYYRGA
 GALLVYDITRRDTFNHLTTWLEDARQHSNSNMVIMLIGNKSDESREVKEEGEAFAREHGLIFMETSARTASNVEEAF
 INTAKEIYEKIQEGVFDINNEANGIKIGPQHAATNASHGGNQQQAGGGCC

Rat 7q DNA (coding 1-639)

ATGGCGTACGCCATCTCTCAAGTACATCATCGGGACACAGGTGTTGGTAATCGTCTTATTGCTACAGTTAC
 AGACAAGAGGTTTCAGCCGGTGCATGACCTCACAAATTGGTGAGAGTTGGTGCCTGAATGATAACCATGGTACAGGGAAAC
 AGATAAAAACCTCAGATCTGGGATACAGCAGGGCAGGACTCTTTCGTTCTATCACAGGTCAATTACAGAGGTCCACCG
 GGGGCTTTACTACTGTATGATATTACAAGGAGAGACACGTTCAACCACCTGGACAACCTGGTTAGAAGACGCCCGTCAGCA
 TTCCAATTCCAACATGGTCATCATGCTTATTGGAAATAAAAGTGACTTGAATCTAGGAGAGAACTGAAAAAGGAAGAG
 GTGAAGCTTTGCACGAGAGCATGGACTTATCTTCATGGAAACTCTGCCAAGACTGCTTCTAATGTAGAGGAGGCATT
 ATTAACACAGCAAAGAAAATTATGAAAAAAATCAAGAAGGGGCTTTGACATTAATAATGAGGCAACGGCATCAAAT
 TGGCCCTCAGCATGCTGCTACCAATGCATCTACCGAGGCACCCAGGAGGGCAGCAGGGAGGGAGGCTGCTGTA

Fig. 33

Rat 19r protein

MVLLKEYRVILPVSVDEYQVGQLYSVAEASKNETGGGEGVVELVNEPYKDDGEKGQYTHKIYHLQSKVPTFVRMLAPEG
 ALNIHEKAWNAYPYCRTVITNEYMKEDFLIKIETWHKPDLGTQENVHKEPEANWKVEAIYIDIAERSQVLSKDYKAEEED
 PAKFKSIKTGRGPLGPWNKQELVNQKDCPYMCAYKLTVFKWGLQNKVENFIHKQEKRIFTNFHRLFTQFCWLKDKNVDLT
 MDDIRRMEEETKRQLDEMQRQKDPVKGMTADD

Rat 19r DNA (coding 1-816)

ATGGTGCTGCTCAAGGAATATCGGTCATCCTGCCCTGTGCTGTAGATGAGTATCAAGTGGGGCAGCTGTACTCTGTGGC
 TGAAGCCAGTAAATGAACACTGGTGGGGAGGTGTGGAGGTCTGGTGAACGAGCCCTACAGAGGATGATGGCG
 AGAAAGCCAGTACACACAAAGATCTACCACTTACAGAGCAAAGTTCCCACCTTGTTCGAATGCTGGCCCCAGAACGC
 GCCCTGAATAATACATGAGAAAAGCCCTGGAATGCCCTACCCCTACTCGACAACGTTATTACAAATGAGTACATGAAGGA
 GAGA
 CTTTCTCATTAACCTGGCACAAGCCAGACCTTGGCACCCAGGAGAATGTGCATAAAACTGGAGGCTGAGGCAT
 GGAAACATGTGGAAAGCTATATATAGACATCGCTGATCGAACGCCAGTACTTAGCAAGGATTACAAGGCAGAGGAAGAC
 CCAGCAAAATTAAATCTATCAAAACAGGACGAGGACCATGGGCCGAATTGGAAAGCAAGAACACTTGTCAATCAGAAGGA
 CTGCCCCATATATGTGTGCATACAAACTGGTTACTGTCAAGTTCAAGTGGTGGGGCTTGCAAGAACAAAGTGGAAAACCTTA
 TACATAGCAAGAGAAAGCCTCTGTTAACAACTTTCACAGGCAGCTGTTCTGTTGGCTTGATAAAATGGGTTGATCTGACT
 ATGGATGACATTGGAGGATGGAAGAGACGAAGACAGCTGGATGAGATGAGACAAAAGGACCCGTGAAAGGAAT
 GACAGCAGATGACTAG

Fig. 34

Monkey KChIP4c (jlkxa053c02) DNA sequence (CD: 122-811)

CGCTCTCCCTCCCCCTTCTAGCAGTAGCCTCTTAATGTAGTTAAAGGCTTACAAAGAAAGCCAGGCAGGGAG
 CACTCTCAGTGGCTGGCGGACCATGACCTAGCTGACCATACTGGAAAGGGCTTGAAATGATAGCAGTTCTGATC
 GTCATGGCTTTGTTAAATTATTGGAACAGTTGGGCTGATTTGAAGCAGGTTAGAAGACAGCCTGGAAAGATGAACT
 GGAGATGCCACTGTGAGGATGGCCCTTGAGGCCAGAGCAAATTACCAAGAAAAGACCTTC
 AGATCCTTACAGAGGATTAAAGAACAAATGCCCAAGTGGTGTGTTAAATGAAGAAACCTTCAAGAGAATTACTCGCAG
 TTCTTCCACAGGGAGACTCTACACACATATGCACTTCTGTGATACGGACCAACATGGAGCTGTGAG
 TTTGGAGGATTCTCATCAAGGTTCTCCATTGGCTCGGGGAGCTACAGAAAACATCTGGAATTAAATCTGT
 ATGATATAAAAGATGGCTACATCACTAAAGAGAAATGCTGTGATAATGAAGCAATATACGACATGATGGTAA
 TGTCACATTCCTGCTCTGGAAAGATGCGCACAGAACACCTGGCAACATTTCAGAAAAGACAAAAAAAGA
 TGGGGTTACCATAGATGAGTTGGAAAGATGTCACAAAAGATGAAATGCTCCAGGCTTGGGATTTGAGGTTTC
 ATGTTGATTAACTCTCAAGTCTGAGTCTGAAAGATGTCACAAAAGATGAAAATATGCGTCCATCAGCTTGGGAA
 CACTTTAGCATAGATTGCTCAGCTGACACTGAAGCAATTATGCAAAAGCTTGTGTTAAATAAAGCAATCCCCA
 AAAGATTTGAGTTCTGATGTTAAATTGCTACATTCATAATGGCACTGAGTTCATGGGATGTTCAACTATTCTCA
 TACTCTGTGAAATTCAAAAGTAATGAGTCTGCAATTGTTTATTGATTCCTTAGCCATGGGATTATGGAGGTTTC
 ACATATCATGATTAAATACAGTGTGTTTGTACTCATTGATGTTAGTCTAGCCTAGGATTGATGGTTTC
 TAATATACTGACATCTGATTAAATTCCAGAAATTAAATTAAATTCTGATGCTGAAATGCTTAATTCTCATTTATFACT
 TTAACTAAACAATAAAGATTAACATGCAATTAAACATGTTCAAGGCTTGTGTTAAATGCTTAATTCTCATTTAGAA
 ATTAAATTCTGTTATTAAACATTAAATTCTCATGATATGCTGAACTTCTGCAATTGCTTAATTGCTTAATTGCTAATGAAAC
 TTAAATAAGCATTTAATTTCATCATACATTATAGTCAGGCTATATACATATATATGCTTAATTGCTGTTAACTTCA
 CAGGGCTGTTTCCATTGATCATCAAGTGGAAAGTCAGGCTACAGGCAATACAAAGGATGTTACAGACATATGCAA
 AGGGCTGAGGATATCTCCAGTATATGCTTAATCAAGTAATCTGCAATTAAAGCAAGGCTTGTGTTAACTCTGTC
 CTCTTCTCTGACTCTTACAGCATTTTACAGCAATTGCAAGGCAAAAGAACCTTGACTACCCACTGTCT
 ACTAGGAACAAACAAACAGCAAGCAAATTCACTTTGAAAGCACCAGTGTGTTCTACATTGACAATACTACCAAGAT
 TCAGTAGAAAATAAGTGTCAACAACTTCAAGGCTTACATATTGTTAGTGTGATCATAAATTCTCAACAAATTCTGAGAT
 ATTCTTAACTCAGCAGCAACACTGTAAGTGTGCAATTACTAAAGACACACATCTGCTCTGTTGTGAGAATATT
 CACAAAGACCAAGGGCTACAGAAGGGAGAAATTGCAACTGTCTTGCACAAATAATCAGGTATCTTGTGTTAG
 AGATAGGATGTTGAAAGCTGCCCTGTTACCCAGTGTAGAAATTAAAGACTGAACTACATGTAACACTGAAATTGCC
 ATCCGGTTGTGAAACTCAATGTGCAATTGTTGATTTCAAAAGAAAATAAGCAAAATAATGTTTAAC
 TCTAAAAAAAAAAAAAA

Monkey KChIP4c protein sequence

MNLEGLEMIAVLIVLIVLFVKLLEQFGLIEAGLDSVEDELEMATVRHRPEALELLAQSKFTKELQILYRGFKNECPG
 VVNEETFKEIYSQFFPQGDSTTYAHFLNFADTDHNGAVSFEDFIKGLSILLRGTVQEKLNWAFNLYDINKGYITKEEM
 LDIMKAIYDMMGKCTYPVLEDAPRQHETTQKMDKNKGDVVTIDEFIESCQKDENIMRSMLFENVI.

Fig. 35

Monkey KChIP4d (jlkx015b10) DNA sequence (CD:64-816)

GTCGACAGACGCCCTGGCCGGTGGACTCCCTGACTCTTACTCCTGCACCCCTCGTCCCCAGACATGAATGTGAGGAGAGT
 GGAAACGCAATTCCGGCTCAGCTGGAGGAGGGCAGCTCCACAGGGGGTTTCTGTATGCTCAGAACAGCACCAAGGCCAGCA
 TTAAAGAGCGCTCATGAAGCTCTGCCCTGCTCAGCTGCCAAAACATCGTCTCTGCTATTCAAACAGCGTGGAGAT
 GAACTGGAGATGGCAGCTGCTAGGCATGGCTGAGGCCCTTGAGCTCTGGAAGGCCAGAGCAAATTACCAAGAAGA
 GCTTCAGATCCTTAACAGGAGATTAAAGAACATGCCCAGTGTGTTAATGAAGAAACCTTCAAAAGAGATTAACT
 CGCAGTCTTCCACAGGGAGACTTACAACATATGCCAATTCTCTGCTCAGTGGCTTGATAACGGACCCAATGGAGCT
 GTGAGTTGAGGAAATTCTCATCAAAGCTTCTCATTTGCTCCGGGGAGCTAACAGAAAAACTCAATTGGGCAATTAA
 TCTGTATGATATAAAAGATGGCTACATCACTAAAGAGGAATGCTTGATATAATGAAGAACATACAGACATGATGG
 GTAAATGATACATATCCTGCTCAGAAGAGATGCCAGACACAGCTGAAACATTTTCAAGAAATGGGAAAAAT
 AAAGATGGGTGTTAGATGAGTCTGAAAGCTCAGAACAGAACATAATGCCCTCCATGCAGCTT
 TGAAAATGTTAGTTAACTGTCAACTGATCTGAATCAGAACAGAACATGTGAACTATTACACCCCTTAAAGTCGGA
 GCTACCACTTGTAGCATAGATTGCTCAGCTGACACTGAAGCATATTATGCCAACAGCTTGTGTTTAATAAAGCAAT
 CCCCAAAAGTTGAGTTCTCAGTTATAATTGCTCCTCCATGCCAACATGCCCTGAGTTCTGGATGTTCTGACTCA
 TTTCATACTCTGTGAATATTGCTAAAGCTAATGCTGATAGTTTATGTTCTGCTACTCATTGTTGATGTTCTGG
 CTTTCACATATCAGTGAATTAAACACAGTGTGTTCTGCTACTCATTGTTGATGTTCTGGATGTTCTGG
 TTTCTAATTAATGACATCTGCATTAAATTCCAGAAATTAAATTAAATTCTGCTGAATGCTGTTAATTTCCATT
 ATACTTAACTGAACTTAAAGATTAACATGCTACTGCTAACATTAAACACATGCTGCTGCTGCTGCTGCTGCT
 TAGAAATTAAATTCTGTTTGTAAACATTAAAGCTTAACTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
 GAAACTTAAATGACATTAATTCTCATACATATTAGTCAGGCCTATTAATGCTGCTGCTGCTGCTGCTGCT
 TCTTACAGGGCTGTTTCTGTTGATCATCAACTGGAAACTTCAGGCCATCAACAAACAAAGGTGTTCTGAGACATA
 TGCAAGGGTCAAGGATATCTATCCCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
 CTGCT
 TGCT
 AAGATTCTAGAGAAATTAACTGCTCAACAACTACAGATTGAAAGCACAGTGTGCTGCTGCTGCTGCTGCT
 AGATTATTCTTAACTCCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
 AATATCACAAGACCAAGAGGCTACAGAAGGGAAATTGCAACTGCTTGTGCAAAATAATCAGGTATGTTCTG
 TGTAGAGATAGGGATGTTGAAAGCTGCCCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCTGCT
 TTGCCATGCCGTGTTGTTGAAACTCAATGTGCACTATTGTTGATTTCAAAAGAAAAATAAAAGCAAAATTTGTTA
 AAAAAAAAAAAAAAA

Monkey KChIP4d protein sequence

MNVRRVESISAQLEEASSSTGGFLYAQNSTRRSIKERLMKLLPCSAAKTSSPAIQNSVDELEMMATVRHRPEALELLEAQSQ
 KFTKKELQILYRGPNECPGVVNEETFKELYSQFFPQGDSTTYAHFLFNAFDTDENGAVSFEDFTKGLSILLRGTVQEK
 LNWFNWLNDINKDGYITKEEMLDIMKAYDMMGKCTYPVLKEDAPRQHVTFFQKMDKNKGVVTFDEFIESCQKDENIM
 RSMQLFVENI.

Fig. 36

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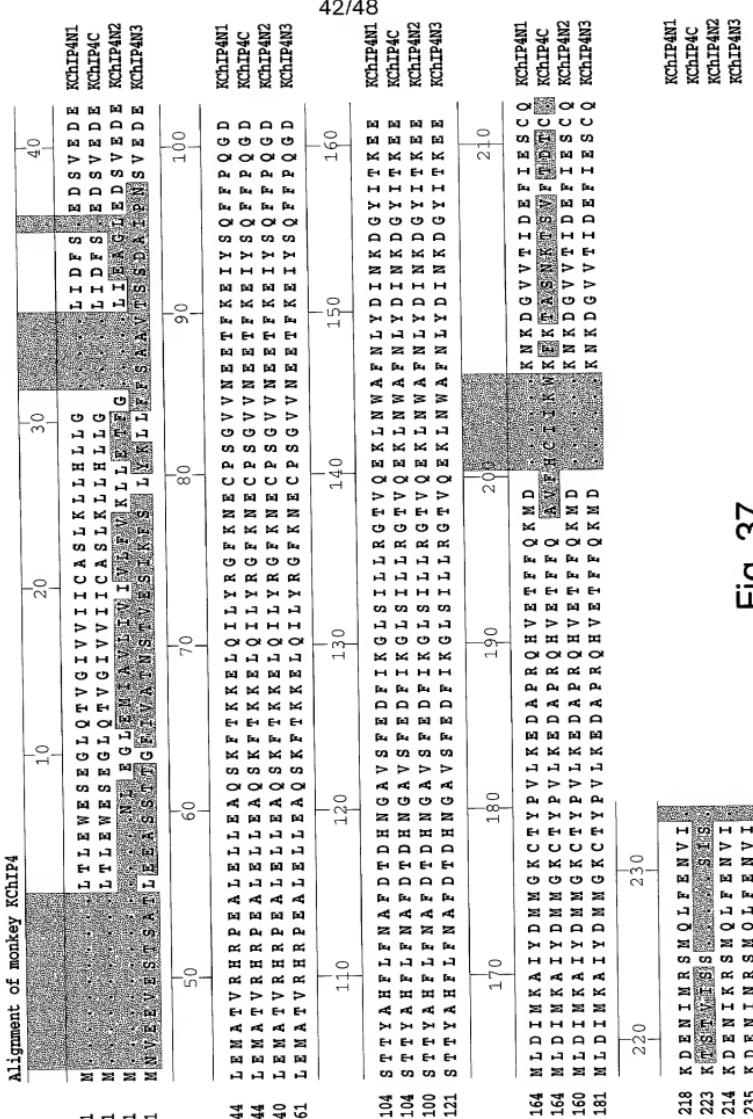
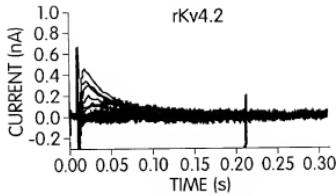


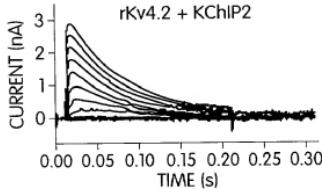
Fig. 37

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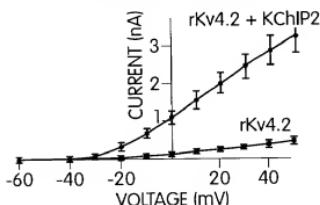
rKv4.2



rKv4.2 + KChIP2



VOLTAGE-DEPENDENCE

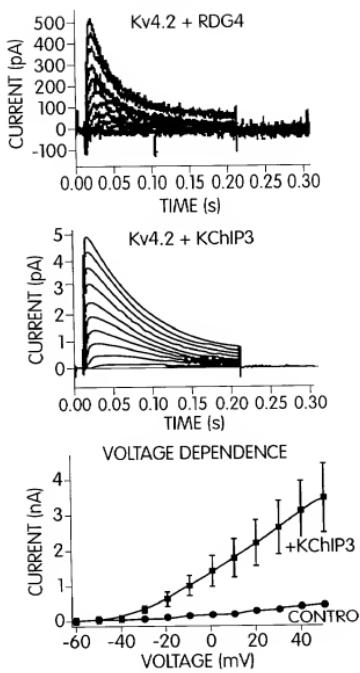


CURRENT PARAMETER	CHO	
	rKv4.2	rKv4.2 + KChIP2
PEAK CURRENT (nA/cell, at 50 mV)	0.51 ±0.098	3.3 ±0.45
PEAK CURRENT DENSITY (pA/pF, at 50 mV)	18.6 ±2.8	196.6 ±26.6
INACTIVATION TIME CONSTANT (ms, at 50 mV)	28.47 ±3.5	95.14 ±8.3
RECOVERY FROM INACTIVATION TIME CONSTANT (ms, at -80 mV)	257.9	49.5
ACTIVATION V _{1/2} (mV)	20.5	-2.2
STEADY-STATE INACTIVATION V _{1/2} (mV)	-47.1	-45.7

Fig. 38

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CURRENT PARAMETER	CHO	
	rKv4.2 +RBG4	rKv4.2 +KChIP3
PEAK CURRENT (nA/cell, at 50 mV)	0.46 ±0.084	3.5 ±0.99
PEAK CURRENT DENSITY (pA/pF, at 50 mV)	29.7 ±11.2	161.7 ±21.8
INACTIVATION TIME CONSTANT (ms, at 50 mV)	29.5 ±9.5	67.2 ±14.1
RECOVERY FROM INACTIVATION TIME CONSTANT (ms, at -80 mV)	435.9	130.8
ACTIVATION V _{1/2} (mV)	4.1	6.1

Fig. 39

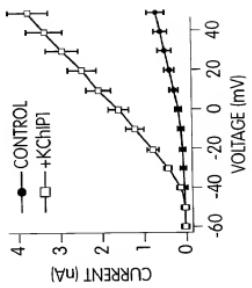


Fig. 40C

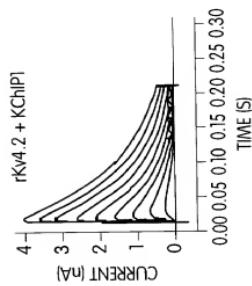


Fig. 40B

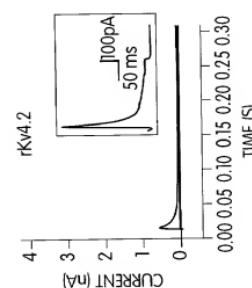


Fig. 40D

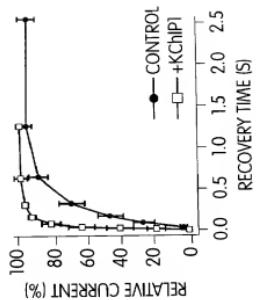


Fig. 40F

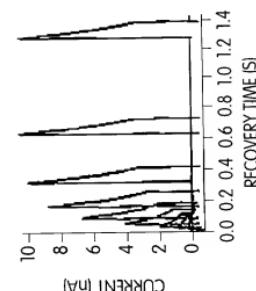


Fig. 40E

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h KCHIPI1 MCA - - - - - D K I E D E L E M T N V C H R P E G L E Q L E A Q T N F T K R E L Q V L Y R G F K P Q V V N E D T F K
 h KCHIPI2 M R G S L S D S R D L D G S Y Q P R L S R Q A L M R C C L V K W I L S S T
 h KCHIPI3 M - - - - - T R A S D G S L L G H P L S K K E G I K W Q R P R L S R Q A L M R C C L V K W I L S S T
 h HIP M G K Q N S K - - - - -
 r NC51 M G K S N S K - - - - -

EF1 X Y Z -Y -X -Z

h KCHIPI1 MCA - - - - - D K I E D E L E M T N V C H R P E G L E Q L E A Q T N F T K R E L Q V L Y R G F K P Q V V N E D T F K
 h KCHIPI2 M R G S L S D S R D L D G S Y Q P R L S R Q A L M R C C L V K W I L S S T
 h KCHIPI3 M - - - - - T R A S D G S L L G H P L S K K E G I K W Q R P R L S R Q A L M R C C L V K W I L S S T
 h HIP M G K Q N S K - - - - -
 r NC51 M G K S N S K - - - - -

EF2 X Y Z -Y -X -Z

h KCHIPI1 Q I Y A Q F P R H G D A S T Y A H Y L F N A F D T T Q T C S V K F E D F V T A L S I L L R G T V H E K L R W T F N L Y D
 h KCHIPI2 Q I Y A Q F P Q G D S S N Y D G S V S E D F V A G L S V I L L R G T V H E K L R W T F N L Y D
 h KCHIPI3 Q I Y A Q F P Q G D A S T Y A H Y L F N A F D T D G N G A I H F E D F V V G L S V T S F G R L E Q R L F I D F E P I I Q S V T S R G T V H E K L R W T F N L Y D
 h HIP K I Y A N F F P Y G D A S K E A H V V R T F D T N S D G T I D F E P I I Q S V T S R G T V H E K L R W T F N L Y D
 r NC51 K I Y K Q F F P F G D P T K F A T F V F N V P D E N K D G R I E F F E P I I Q S V T S R G T V H E K L R W T F N L Y D

EF3 X Y Z -Y -X -Z

h KCHIPI1 N K D G Y I N K E E M M D I V K A I Y D M M G K Y T P V L K E D D T P R O H V D V F F Q K N D K N K D G G V U T L D E F
 h KCHIPI2 N K D G Y I N K E E M M D I V K A I Y D M M G K Y T P V L K E D D T P R O H V D V F F Q K N D K N K D G G V U T L D E F
 h KCHIPI3 N K D G Y I N K E E M M D I V K A I Y D M M G K Y T P V L K E D D T P R O H V D V F F Q K N D K N K D G G V U T L D E F
 h KCHIPI1 N K D G C I T K E E M L D M M G K Y T P V L K E D D T P R O H V D V F F Q K N D K N K D G G V U T L D E F
 h KCHIPI2 N K D G C I T K E E M L D M M G K Y T P V L K E D D T P R O H V D V F F Q K N D K N K D G G V U T L D E F
 h KCHIPI3 N K D G C I T K E E M L D M M G K Y T P V L K E D D T P R O H V D V F F Q K N D K N K D G G V U T L D E F
 h HIP L D G N G Y I S R E E N L E I V Q A I Y K M V S S V M K N P D E D S T P E K R T E K I F R Q M D T N N D G K L S L Q E E F
 r NC51 L D N D G Y I T R N E M D I V D A I Y Q M V G N T V E L P E E E N T P E K R V D R I F A M M D K N A D G K L T L Q E F

EF4 X Y Z -Y -X -Z

h KCHIPI1 L E S C Q E D D N I M R S L Q - - - - - L F Q N V M .
 h KCHIPI2 L E S C Q E D D N I M R S L Q - - - - - L F D N V I .
 h KCHIPI3 L E A C Q E D D N I M R S L Q - - - - - L F E N V I .
 h HIP I R G S K A D P S I V Q A L C D P S S R S Q F .
 r NC51 Q E G S K A D P S I V Q A L C D P S S R S Q F .
 r NC51 S L Y D G L V .

Fig. 41

8963 • J. Neurosci., June 16, 2010 • 30(24):8958–8963

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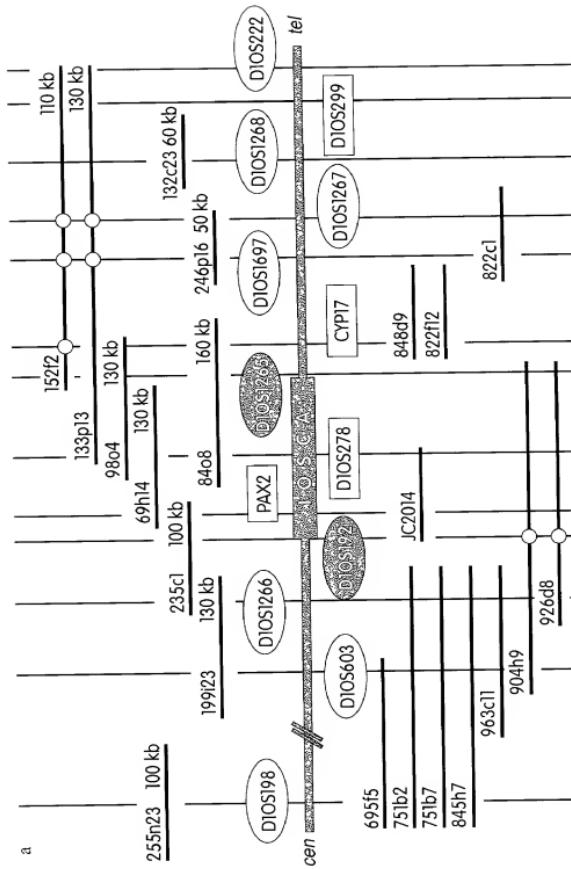


Fig. 42

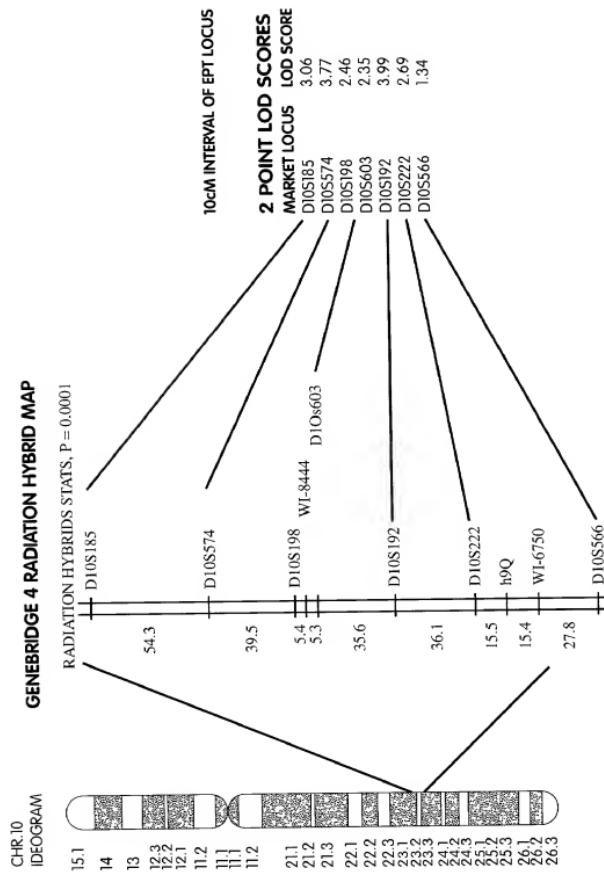


Fig. 4.3

Attorney's
Docket
Number MNI-070CP4

Declaration, Petition and Power of Attorney
for Continuation-in-Part Patent Application

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR

the specification of which

(check one)

is attached hereto.

was filed on _____ as

Application Serial No. _____

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

This application in part discloses and claims subject matter disclosed in my earlier filed application(s), as follows:

Serial No.60/110,033, filed November 25, 1998;
 Serial No.60/109,333, filed November 20, 1998;
 Serial No.60/110,277, filed November 30, 1998, as to which I claim priority benefit under Title 35, United States Code, §119(e).

Serial No.09/298,731, filed April 23, 1999;
 Serial No.09/350,614, filed July 9, 1999;
 Serial No.09/350,874, filed July 9, 1999;
 Serial No.09/399,913, filed September 21, 1999;
 Serial No.09/400,492, filed September 21, 1999, as to which I claim priority benefit under Title 35, United States Code, §120.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56, including all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of the continuation-in-part application.

DD-2250-95/202960

AS TO PARENT APPLICATION:

As to the subject matter of this application which is common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to said earlier application, or in public use or on sale in the United States of America more than one year prior to said earlier application; that the common subject matter has not been patented or made the subject of an inventor's certificate issued before the date of said earlier application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to said earlier application; and

As to applications for patents or inventor's certificate or PCT international application(s) designating at least one country other than the United States of America, on the common subject matter, filed in or designating any country foreign to the United States of America, prior to said earlier application by me or my legal representatives or assigns,

Check one:

X no such applications have been filed.

_ such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO SAID EARLIER U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
			<u>_</u> Yes <u>_</u> No <u>_</u>
			<u>_</u> Yes <u>_</u> No <u>_</u>
			<u>_</u> Yes <u>_</u> No <u>_</u>
			<u>_</u> Yes <u>_</u> No <u>_</u>
			<u>_</u> Yes <u>_</u> No <u>_</u>

ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO SAID EARLIER U.S. APPLICATION

AS TO THIS APPLICATION:

As to the subject matter of this application which is not common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof, or more than one year prior to this application, or in public use or on sale in the United States of America more than one year prior to this application; that said non-common subject matter has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to this application; and

As to applications for patents or inventor's certificate or PCT international application(s) designating at least one country other than the United States of America, on said non-common subject matter, filed in or designating any country foreign to the United States of America, prior to this application by me or my legal representatives or assigns,

Check one:

 no such applications have been filed.

such applications have been filed as follows

EARLIEST FOREIGN APPLICATION(S), IF ANY, FILED WITHIN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

Country	Application Number	Date of Filing (month,day,year)	Priority Claimed Under 35 USC 119
PCT	PCT/US99/27428	11/19/99	<u>X</u> Yes <u> </u> No <u> </u>
			<u> </u> Yes <u> </u> No <u> </u>
			<u> </u> Yes <u> </u> No <u> </u>
			<u> </u> Yes <u> </u> No <u> </u>
			<u> </u> Yes <u> </u> No <u> </u>

ALL FOREIGN APPLICATION(S), IF ANY, FILED MORE THAN 12 MONTHS
(6 MONTHS FOR DESIGN) PRIOR TO THIS U.S. APPLICATION

CLAIM FOR BENEFIT OF U.S. PROVISIONAL APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

<u>60/110,033</u> (Application Serial No.)	<u>November 25, 1998</u> (Filing Date)
<u>60/109,333</u> (Application Serial No.)	<u>November 20, 1998</u> (Filing Date)
<u>60/110,277</u> (Application Serial No.)	<u>November 30, 1998</u> (Filing Date)

CLAIM FOR BENEFIT OF U.S. PATENT APPLICATION(S)

I hereby claim the benefit under 35 U.S.C. §120 of any United States patent application(s) listed below.

<u>09/298,731</u> (Application Serial No.)	<u>April 23, 1999</u> (Filing Date)
<u>09/350,614</u> (Application Serial No.)	<u>July 9, 1999</u> (Filing Date)
<u>09/350,874</u> (Application Serial No.)	<u>July 9, 1999</u> (Filing Date)
<u>09/399,913</u> (Application Serial No.)	<u>September 21, 1999</u> (Filing Date)
<u>09/400,492</u> (Application Serial No.)	<u>September 21, 1999</u> (Filing Date)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the Patent and Trademark Office connected therewith.

James E. Cockfield	Reg. No. 19,162	Nicholas P. Trianio III	Reg. No. 36,397
Thomas V. Smurzynski	Reg. No. 24,798	Peter C. Lauro	Reg. No. 32,360
Ralph A. Loren	Reg. No. 29,325	DeAnn F. Smith	Reg. No. 36,683
Giulio A. DeConti, Jr.	Reg. No. 31,503	William D. DeVaul	Reg. No. 42,483
Ann Lampert Hammitt	Reg. No. 34,858	David J. Rikkers	Reg. No. 43,882
Elizabeth A. Hanley	Reg. No. 33,505	Chi Suk Kim	Reg. No. 42,728
Amy E. Mandragouras	Reg. No. 36,207	Maria C. Laccotripe	Limited Recognition
Anthony A. Laurentano	Reg. No. 38,220		Under 37 C.F.R. § 10.9(b)
Jane E. Remillard	Reg. No. 38,872	Debra J. Milasincic	Reg. No. P46,931
Jeremiah Lynch	Reg. No. 17,425	David R. Burns	Reg. No. P46,590
Kevin J. Canning	Reg. No. 35,470	Sean D. Detweiler	Reg. No. 42,482
Jeanne M. DiGiorgio	Reg. No. 41,710	Peter S. Stecher	Reg. No. P47,259
Megan E. Williams	Reg. No. 43,270		

all of: LAHIVE & COCKFIELD, LLP, 28 State Street, Boston, MA 02109

and to: Jean M. Silveri Reg. No. 39,030 Mark F. Boshar Reg. No. 35,456
Theodore Allen Reg. No. 41,578 Scott A. Brown Reg. No. 32,724
Jill E. Uhl Reg. No. 43,213

of: Millennium Pharmaceuticals, Inc., 75 Sidney Street, Cambridge, MA 02139

Send Correspondence to Amy E. Mandragouras at **Customer Number 000959** whose address is:

Lahive & Cockfield, LLP, 28 State Street, Boston, MA 02109

Direct Telephone Calls to: (name and telephone number)

Amy E. Mandragouras, (617) 227-7400

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor Kenneth Rhodes	Date
Inventor's signature	
Residence 808 Atkinson Circle, Neshanic Station, NJ 08853	
Citizenship U.S.	
Post Office Address (if different)	

Full name of second inventor, if any Maria Betty	Date
Inventor's signature	
Residence 116 S. Brentwood Drive, Mt. Laurel, NJ 08853	
Citizenship U.K.	
Post Office Address (if different)	

Full name of third inventor, if any Huai-Ping Ling	Date
Inventor's signature	
Residence 17 Wellesley Court, Princeton Junction, NJ 08550	
Citizenship U.S.	
Post Office Address (if different)	

Full name of fourth inventor, if any Wenqian An	Date
Inventor's signature	
Residence 1500 Worcester Rd. Apt. #212, Framingham, MA 01702	
Citizenship U.S.	
Post Office Address (if different)	

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Kenneth Rhodes *et al.*

Serial No.: N/A

Filed: Herewith

For: *POTASSIUM CHANNEL INTERACTORS AND USES THEREFOR*

Attorney Docket No.: MNI-070CP4

Assistant Commissioner for Patents
Box Sequence
Washington, D.C. 20231

TRANSMITTAL LETTER FOR DISKETTE CONTAINING SEQUENCE LISTING

Dear Sir:

Enclosed is a diskette which contains a computer readable form of the Sequence Listing for the patent application filed herewith. The Sequence Listing complies with the requirements of 37 C.F.R. § 1.821. The material on this diskette is identical in substance to the sequence listing appearing on pages 1-92 of the Sequence Listing which is submitted herewith, as required by 37 C.F.R. § 1.821(f). The computer readable form of the Sequence Listing contained on the enclosed diskette is understood to comply with the requirements of § 1.824(d).

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Signature

Nelson Barros

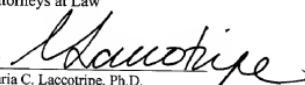
Nelson F. Barros

Please Print Name of Person Signing

LAHIVE & COCKFIELD, LLP

Attorneys at Law

By


Maria C. Laccotripe, Ph.D.
Agent for Applicants

Limited Recognition Under 37 C.F.R. §10.9(b)

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002260-052786

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Betty, Maria
Ling, Huai-Ping
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DRAFT - 09/26/2000

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 acc aaa caa agg cga ccc tct aaa gac atc gcc tgg tgg tat tac cag 160			
Thr Lys Gln Arg Arg Pro Ser Lys Asp Ile Ala Trp Trp Tyr Tyr Gln			
15 20 25			
 tat cag aga gac aag att gag gat gag cta gag atg acc atg gtt tgc 208			
Tyr Gln Arg Asp Lys Ile Glu Asp Glu Leu Glu Met Thr Met Val Cys			
30 35 40			
 cac cgg cct gag gga ctg gag cag ctt gag gca cag acg aac ttc acc 256			
His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr			
45 50 55 60			
 aag aga gaa ctg caa gtc ttg tac cgg gga ttc aaa aac gag tgc cct 304			
Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro			
65 70 75			
 agc ggt gtg gtc aat gaa gaa aca ttc aag cag atc tac gct cag ttt 352			
Ser Gly Val Val Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe			
80 85 90			
 ttc cct cac gga gat gcc agc aca tat gca cat tac ctc ttc aat gcc 400			
Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala			
95 100 105			
 ttc gac acc acc cag aca ggc tct gta aag ttc gag gac ttt gtg act 448			
Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr			
110 115 120			
 gct ctg tcg att tta ctg aga ggg aca gtc cat gaa aaa cta agg tgg 496			
Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp			
125 130 135 140			
 acg ttt aat ttg tat gac atc aat aaa gac ggc tac ata aac aaa gag 544			
Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu			
145 150 155			

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gag atg atg gac ata gtc aaa gcc atc tat gac atg atg ggg aaa tac 592
Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr
      160       165       170

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acc tat cct gtg ctc aaa gag gac act ccc agg cag cat gtg gat gtc 640
Thr Tyr Pro Val Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val
      175          180          185

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ttc ttc cag aaa atg gat aaa aat aaa gat ggc att gta acg tta gat 688
Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp
 190          195          200

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gaa ttt ctt gaa tca tgt cag gag gat gac aac atc atg aga tct cta 736
Glu Phe Leu Glu Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu
205      210          215          220

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cag ctg ttc caa aat gtc atg taactggaga cactggccat tctgtctca 787
Gln Leu Phe Gln Asn Val Met
225

gagacactga caaacacctt aatggccctga tctggcccttg ttccaaattt acacaccaac 847
tctgggaca gaaataccctt ttacactttg gaagaattct ctgtctgaaa ctttctacaa 907
aacctggcac cacgtggcgc tgctctgag ggacgaggcg agatccgact ttgttttgg 967
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<212> PRT
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Lys Ile Glu Asp Glu Leu Glu Met Thr Met Val Cys His Arg Pro Glu
35 40 45

Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu Leu
50 55 60
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val
65 70 75 80

Asn Glu Glu Thr Phe Lys Gln Ile Tyr Ala Gln Phe Phe Pro His Gly
85 90 95

Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr Thr
100 105 110

Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser Ile
115 120 125

Leu Leu Arg Gly Thr Val His Glu Lys Leu Arg Trp Thr Phe Asn Leu
130 135 140

Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Glu Met Met Asp
145 150 155 160

Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Val
165 170 175

Leu Lys Glu Asp Thr Pro Arg Gln His Val Asp Val Phe Phe Gln Lys
180 185 190

Met Asp Lys Asn Lys Asp Gly Ile Val Thr Leu Asp Glu Phe Leu Glu
195 200 205

Ser Cys Gln Glu Asp Asp Asn Ile Met Arg Ser Leu Gln Leu Phe Gln
210 215 220

Asn Val Met
225

<210> 11
<211> 955
<212> DNA
<213> Rattus sp.

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<221> CDS
<222> (345)..(953)

<220>
<223> Xaa at position 92 of the corresponding amino acid
sequence may be any amino acid

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tagttctttt ggcttagcaga tggtagggaa ctggtaagg ctttggagaa attaccttag 120
gaaaacgggg aaataaaagc aaagattacc atgaattgca agattaccta gcaattgcaa 180
ggtagggaga gagagggtggaa gggcggagta gacaggaggg agggagaaag tgagagggaa 240

DRAFT DRAFT DRAFT DRAFT

ccatggctgtt	ggaataacc	ctgcacttgg	aacagcggca	aagaagcgcg	atttccagc	300
tttaaatgcc	tccccgcgtt	ctgcttgctt	accggaaac	ggag	atg ttg acc cag	356
					Met Leu Thr Gln	
					1	
ggc gag tct gaa ggg ctc cag acc ttg ggg ata gta gtc gtc ctg tgt						404
Gly Glu Ser Glu Gly Leu Gln Thr Leu Gly Ile Val Val Val Leu Cys						
5	10	15	20			
tcc tct ctg aaa cta ctg cac tac ctc ggg ctg att gac ttg tcg gat						452
Ser Ser Leu Lys Leu Leu His Tyr Leu Gly Leu Ile Asp Leu Ser Asp						
25	30	35				
gac aag atc gag gat gat ctg gag atg acc atg gtt tgc cat cgg cct						500
Asp Lys Ile Glu Asp Asp Leu Glu Met Thr Val Cys His Arg Pro						
40	45	50				
gag gga ctg gag cag ctt gag gca cag acg aac ttc acc aag aga gaa						548
Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe Thr Lys Arg Glu						
55	60	65				
ctg caa gtc ctt tac cgg gga ttc aaa aac gag tgc ccc agt ggt gtg						596
Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val						
70	75	80				
gtt aac gaa gag aca ttc aag cng atc tac gct cag ttt ttc cct cat						644
Val Asn Glu Glu Thr Phe Lys Xaa Ile Tyr Ala Gln Phe Pro His						
85	90	95	100			
gga gat gcc agc aca tac gca cat tac ctc ttc aat gcc ttc gac acc						692
Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn Ala Phe Asp Thr						
105	110	115				
acc cag aca ggc ttc gta aag ttc gag gac ttt gtg act gct ctc tgc						740
Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val Thr Ala Leu Ser						
120	125	130				
att tta ctg aga gga acg gtc cat gaa aaa ctg aag tgg acg ttt aat						788
Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Lys Trp Thr Phe Asn						
135	140	145				
ttg tac gac atc aat aaa gac ggc tac ata aac aaa gag gag atg atg						836
Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys Glu Met Met						
150	155	160				
gac ata gtg aaa gcc atc tat gac atg atg ggg aaa tac acc tat ctt						884
Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Leu						
165	170	175	180			
gtg ctc aaa gag gac act tcc agg cag cac gtg gac gtc ttc ttc cag						932
Val Leu Lys Glu Asp Thr Ser Arg Gln His Val Asp Val Phe Phe Gln						
185	190	195				
aaa atg gat aaa aat aaa gat gg						955
Lys Met Asp Lys Asn Lys Asp						
200						

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<212> PRT
<213> Rattus sp.

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Val Val Leu Cys Ser Ser Leu Lys Leu Leu His Tyr Leu Gly Leu Ile
20 25 30

Asp Leu Ser Asp Asp Lys Ile Glu Asp Asp Leu Glu Met Thr Met Val
35 40 45

Cys His Arg Pro Glu Gly Leu Glu Gln Leu Glu Ala Gln Thr Asn Phe
50 55 60

Thr Lys Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys
65 70 75 80

Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Xaa Ile Tyr Ala Gln
85 90 95

Phe Phe Pro His Gly Asp Ala Ser Thr Tyr Ala His Tyr Leu Phe Asn
100 105 110

Ala Phe Asp Thr Thr Gln Thr Gly Ser Val Lys Phe Glu Asp Phe Val
115 120 125

Thr Ala Leu Ser Ile Leu Leu Arg Gly Thr Val His Glu Lys Leu Lys
130 135 140

Trp Thr Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Asn Lys
145 150 155 160

Glu Glu Met Met Asp Ile Val Lys Ala Ile Tyr Asp Met Met Gly Lys
165 170 175

Tyr Thr Tyr Leu Val Leu Lys Glu Asp Thr Ser Arg Gln His Val Asp
180 185 190

Val Phe Phe Gln Lys Met Asp Lys Asn Lys Asp
195 200

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<211> 2009
<212> DNA
<213> Homo sapiens

<220>
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<222> (207)..(1016)

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ccgcgcagggg ggcgcgtgtg agcgccttat cccggccacc cggcgcccccc tccccacggcc 180

cgggcgggag cggggcgccg ggggcc atg cgg ggc cag ggc cgc aag gag agt 233
 Met Arg Gly Gln Gly Arg Lys Glu Ser
 1 5

ttg tcc gat tcc cga gac ctg gac ggc tcc tac gac cag ctc acg ggc 281
 Leu Ser Asp Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
 10 15 20 25

cac cct cca ggg ccc act aaa aaa gcg ctg aag cag cga ttc ctc aag 329
 His Pro Pro Gly Pro Thr Lys Ala Leu Lys Gln Arg Phe Leu Lys
 30 35 40

ctg ctg ccc tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aca 377
 Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Thr
 45 50 55

tta gcc gcc cca gcc tcc ctc cgc ccc cac aga ccc cgc ctg ctg gac 425
 Leu Ala Ala Pro Ala Ser Leu Arg Pro His Arg Pro Arg Leu Leu Asp
 60 65 70

cca gac agc gtg gac gat gaa ttt gaa ttg tcc acc gtg tgt cac cgg 473
 Pro Asp Ser Val Asp Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg
 75 80 85

cct gag ggt ctg gag cag ctg cag gag caa acc aaa ttc acg cgc aag 521
 Pro Glu Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys
 90 95 100 105

gag ttg cag gtc ctg tac cgg ggc ttc aag aac gaa tgt ccc agc gga 569
 Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
 110 115 120

att gtc aat gag gag aac ttc aag cag att tac tcc cag ttc ttt cct 617
 Ile Val Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro
 125 130 135

caa gga gac tcc agc acc tat gcc act ttt ctc ttc aat gcc ttt gac 665
 Gln Gly Asp Ser Ser Thr Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp
 140 145 150

acc aac cat gat ggc tgc gtc agt ttt gag gac ttt gtg gct ggt ttg 713
 Thr Asn His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu
 155 160 165

tcc gtg att ctt cgg gga act gta gat gac agg ctt aat tgg gcc ttc 761
 Ser Val Ile Leu Arg Gly Thr Val Asp Asp Arg Leu Asn Trp Ala Phe
 170 175 180 185

aac ctg tat gac ctt aac aag gac ggc tgc atc acc aag gag gaa atg 809
 Asn Leu Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met
 190 195 200

ctt gac atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac 857
 Leu Asp Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
 205 210 215

cct gca ctc cgg gag gag gcc cca agg gaa cac gtg gag agc ttc ttc 905
 Pro Ala Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe

08/25/02 95/02/950

220	225	230	
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att gag tct tgtcaa aag gat gag aac atc atg agg tcc atg cag ctc Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu 250 255 260			1001
ttt gac aat gtc atc tagccccag gagagggggt cagtgttcc tggggggacc Phe Asp Asn Val Ile 270			1056
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agtttttgtt tcccatgttc tctatagact tggacacttc ctgaacttg ggcctatcac 1956			
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Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro 35 40 45			

D07250-95707950

Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
 50 55 60

Arg Pro His Arg Pro Arg Leu Leu Asp Pro Asp Ser Val Asp Asp Glu
 65 70 75 80

Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
 85 90 95

Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg
 100 105 110

Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
 115 120 125

Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr
 130 135 140

Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
 145 150 155 160

Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr
 165 170 175

Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys
 180 185 190

Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile
 195 200 205

Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala
 210 215 220

Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys
 225 230 235 240

Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys Asp
 245 250 255

Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
 260 265 270

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<211> 1247

<212> DNA

<213> Rattus sp.

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<221> CDS

<222> (2)..(772)

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 1 5 10 15

ccc agt aaa aaa gcc ctg aag cag cgt ttc ctc aag ctg ctg ccg tgc 97
 Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Pro Cys

DRAFT - USE FOR INFORMATION PURPOSES ONLY

	20	25	30	
tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aca tta gct gcc cca Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro 35 40 45				145
gcc tcc ctc cgc ccc cac aga ccc cgc ccg ctg gac cca gac agc gta Ala Ser Leu Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val 50 55 60				193
gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag ggc ctg Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu 65 70 75 80				241
gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg cag gtc Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val 85 90 95				289
ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc aac gag Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu 100 105 110				337
gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga gac tcc Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser 115 120 125				385
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cgg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta tat gac Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp 165 170 175				529
ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac att atg Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met 180 185 190				577
aag tcc atc tat gac atg atg ggc aag tac aca tac ctc ctt gcc ctc cgg Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg 195 200 205				625
gag gag gcc cca aga gaa cac gtg gag agc ttc ttc cag aag atg gac Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp 210 215 220				673
agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag tct tgt Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys 225 230 235 240				721
caa cag gac gag aac atc atg agg tcc atg cag ctc ttt gat aat gtc Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val 245 250 255				769
atc tagccccca gggagagggg tttagtgtgtc cttaggtgac caggctgtag Ile				822

tccttagtcca gacgaaaccta accctctctc tccaggcctg tcctcatctt acctgtacc 882
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<212> PRT
<213> Rattus sp.

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Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro
35 40 45
Ala Ser Leu Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val
50 55 60
Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
65 70 75 80
Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
85 90 95
Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
100 105 110
Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser
115 120 125
Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp
130 135 140
Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu
145 150 155 160
Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp
165 170 175
Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met
180 185 190
Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg

195	200	205
Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp		
210	215	220

Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys
225 230 235 240

Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val
245 250 255

Ile

<210> 17
<211> 2343
<212> DNA
<213> *Mus musculus*

<220>
<221> CDS
<222> (181)..(990)

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ctatccctggc cacccggcgc cccctccac ggcccaggcg ggaggcggggc gccccggggc 180
atg cgg ggc caa ggc cga aag gag agt ttg tcc gaa tcc cga gat ttg 228
Met Arg Gly Gln Gly Arg Lys Glu Ser Leu Ser Glu Ser Arg Asp Leu
   1          5          10         15

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gac ggc tcc tat gac cag ctt acg ggc cac cct cca ggg ccc agt aaa 276
Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
          20           25           30

```

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aaa gcc ctg aag cag cgt ttc ctc aag ctg ctg ccg tgc tgc ggg ccc 324
Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
          35           40           45

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caa gcc ctg ccc tca gtc agt gaa aca tta gct gcc cca gcc tcc ctc 372
Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
      50          55          60

```

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cgc ccc cac aga ccc cgc ccg ctg gac cca gac agc gtg gag gat gag   420
Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val Glu Asp Glu
       65          70           75          80

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ttt gaa cta tcc acg gtg tgc cac cgg cct gag ggt ctg gaa caa ctc 468
Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
          85           90           95

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cag gaa caa acc aag ttc aca cgc aga gag ttg cag gtc ctg tac aga 516
Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg
   100      105      110

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ggc ttc aag aac gaa tgt ccc agc gga att gtc aac gag gag aac ttc 564
Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe

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gct act ttt ctc ttc aat gcc ttt gac acc aac cat gat ggc tct gtc Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val 145 150 155 160			660
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gac ggc gtg gtg acc att gag gaa ttc att gag tct tgt caa cag gac Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp 245 250 255			948
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212 PBT

<213> Mus musculus

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35 40 45

Gln Ala Leu Pro Ser Val Ser Glu Thr Leu Ala Ala Pro Ala Ser Leu
50 55 60

Arg Pro His Arg Pro Arg Pro Leu Asp Pro Asp Ser Val Glu Asp Glu
65 70 75 80

Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu
85 90 95

Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg
 100 105 110

Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe
 115 120 125

Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr
130 135 140

Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val
145 150 155 160

Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr

165	170	175
Ile Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys 180	185	190

Asp Gly Cys Ile Thr Lys Glu Met Leu Asp Ile Met Lys Ser Ile 195	200	205
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Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala 210	215	220
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Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys 225	230	235	240
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Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp 245	250	255
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Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile 260	265	270
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<211> 1955

<212> DNA

<213> Homo sapiens

<220>

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<222> (207)..(962)

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Met Arg Gly Gln Gly Arg Lys Glu Ser 1 5

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ctg ctg ccc tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn 45 50 55
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ggc ctg gag cag ctg cag gag caa acc aaa ttc acg cgc aag gag ttg Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu 75 80 85
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cag gtc ctg tac cgg ggc ttc aag aac gaa tgt ccc agc gga att gtc 521
 Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val
 90 95 100 105

aat gag gag aac ttc aag cag att tac tcc cag ttc ttt cct caa gga 569
 Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly
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gac tcc agc acc tat gcc act ttt ctc ttc aat gcc ttt gac acc aac 617
 Asp Ser Ser Thr Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn
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 155 160 165

tat gac ctt aac aag gac ggc tgc atc acc aag gag gaa atg ctt gac 761
 Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp
 170 175 180 185

atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac cct gca 809
 Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala
 190 195 200

ctc cgg gag gac gcc cca agg gaa cac gtg gag agc ttc ttc cag aag 857
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atg gac aga aac aag gat ggt gtg acc att gag gaa ttc att gag 905
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 220 225 230

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 Asn Val Ile
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<211> 252

<212> PRT

<213> Homo sapiens

<400> 20

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35 40 45Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Asp Asp Glu Phe Glu
50 55 60Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
65 70 75 80Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
85 90 95Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
100 105 110Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
115 120 125Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
130 135 140Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
145 150 155 160Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
165 170 175Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
180 185 190

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Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
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<210> 21

<211> 2300

<212> DNA

<213> Rattus sp.

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<222> (214)..(969)

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 Met Arg Gly Gln Gly Arg Lys
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 Glu Ser Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu
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acg ggc cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc 330
 Thr Gly His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe
 25 30 35

ctc aag ctg ctg ccc tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt 378
 Leu Lys Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser
 40 45 50 55

gaa aac acg gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga 426
 Glu Asn Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg
 60 65 70

cct gag ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga 474
 Pro Glu Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg
 75 80 85

gag ctg cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg 522
 Glu Leu Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
 90 95 100

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 Ile Val Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro
 105 110 115

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 Gln Gly Asp Ser Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp
 120 125 130 135

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 Thr Asn His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu
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 Ser Val Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe
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 aac tta tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg 762
 Asn Leu Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met
 170 175 180

 ctt gac att atg aag tcc atc tat gac atg atg ggc aag tac aca tac 810
 Leu Asp Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr
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 cct gcc ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc 858
 Pro Ala Leu Arg Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe
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 Gln Lys Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe
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 atc gag tct tgt caa cag gac gag aac atc atg agg tcc atg cag ctc 954
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 Phe Asp Asn Val Ile
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<210> 22
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<212> PRT
<213> *Rattus* sp.

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   35          40          45

Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
   50          55          60

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
   65          70          75          80

Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
   85          90          95

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
  100         105         110

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr Ala Thr
  115         120         125

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
  130         135         140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Ile Asp
  145         150         155         160

Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
  165         170

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp

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195	200	205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly		
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Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp Glu Asn		
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Met Arg Gly Gln Gly Arg Lys Glu Ser						
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ttg tcc gat tcc cga gac ctg gac ggc tcc tac gac cag ctc acg gac	281					
Leu Ser Asp Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Asp						
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agc gtg gac gat gaa ttt gaa ttg tcc acc gtg tgt cac cgg cct gag	329					
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30	35	40				

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Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu						
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cag gtc ctg tac cgg ggc ttc aag aac gaa tgt ccc agc gga att gtc	425					
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val						
60	65	70				

aat gag gag aac ttc aag cag att tac tcc cag ttc ttt cct caa gga	473					
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly						
75	80	85				

gac tcc agc acc tat gcc act ttt ctc ttc aat gcc ttt gac acc aac	521					
Asp Ser Ser Thr Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn						
90	95	100	105			

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His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val						

att ctt cgg gga act gta gat gac agg ctt aat tgg gcc ttc aac ctg Ile Leu Arg Gly Thr Val Asp Asp Arg Leu Asn Trp Ala Phe Asn Leu	110	115	120		
125	130	135	617		
tat gac ctt aac aag gac ggc tgc atc acc aag gag gaa atg ctt gac Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Met Leu Asp	125	140	145	150	665
140	145	150			
atc atg aag tcc atc tat gac atg atg ggc aag tac acg tac cct gca Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala	155	160	165	713	
155	160	165			
ctc cgg gag gag gcc cca agg gaa cac gtg gag agc ttc ttc cag aag Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys	170	175	180	761	
170	175	180	185		
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190	195	200			
tct tgt caa aag gat gag aac atc atg agg tcc atg cag ctc ttt gac Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp	205	210	215	857	
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<212> PRT
<213> Homo sapiens

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Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
35 40 45

Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
50 55 60

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
65 70 75 80

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
85 90 95

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
100 105 110

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
115 120 125

Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
130 135 140

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
145 150 155 160

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
165 170 175

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
180 185 190

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195 200 205

Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
210 215 220

<210> 25
<211> 2191
<212> DNA
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<222> (133)..(792)

<400> 25

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gcgccggggg cc atg	cgg ggc cag	ggc cgc aag	gag agt ttg	tcc gat tcc	171
Met Arg	Gly Gln	Gly Arg	Lys Glu	Ser Leu	Ser Asp Ser
1	5			10	

cga gac ctg gac gga tcc tac gac cag ctc acg gac agc gtg gag gat 219
 Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Asp Ser Val Glu Asp
 15 20 25

gaa ttt gaa ttg	tcc acc gtg	tgt cac cgg	cct gag ggt	ctg gag cag	267
Glu Phe Glu	Leu Ser	Thr Val	Cys His	Arg Pro	Glu Gly Leu Glu Gln
30	35		40		45

ctg cag gag caa acc aaa ttc acg cgc aag gag ttg cag gtc ctg tac 315
 Leu Gln Glu Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr
 50 55 60

cgg ggc ttc aag aac	gaa tgt ccg	agg gga att	gtc aat gag	gag aac	363
Arg Gly Phe Lys	Asn Glu Cys	Pro Ser Gly	Ile Val Asn Glu	Glu Asn	
65	70		75		

ttc aag caa att tac tcc cag ttc ttt cct caa gga gac tcc agc acc 411
 Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr
 80 85 90

tat gcc act ttt ctc ttc aat	gcc ttt gac	acc aac cat	cat gat	ggc tcg	459
Tyr Ala Thr Phe Leu	Phe Asn Ala	Phe Asp Thr	Asn His	Asp Gly Ser	
95	100		105		

gtc agt ttt gag gac ttt gtg gct ggt ttg tcc gtg att ctt cgg gga 507
 Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly
 110 115 120 125

act gta gat gac agg ctt aat tgg	gcc ttc aac	ttg tat gac	ctc aac	555
Thr Val Asp Asp Arg Leu Asn Trp	Ala Phe Asn	Leu Tyr Asp	Leu Asn	
130	135		140	

aag gac ggc tgc atc acc aag gag gaa atg ctt gac atc atg aag tcc 603
 Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser
 145 150 155

atc tat gac atg atg ggc aag	tac aca tac	cct gca ctc	cggtgg	gag	651
Ile Tyr Asp Met Met Gly Lys	Tyr Thr Tyr	Pro Ala	Leu Arg	Glu Glu	
160	165		170		

gcc cca agg gaa cat gtg gag aac ttc ttc cag aag atg gac aga aac 699
 Ala Pro Arg Glu His Val Glu Asn Phe Phe Gln Lys Met Asp Arg Asn
 175 180 185

aag gat ggc gtg gtg acc att gag	gaa ttc att	gag tct tgc	caa aag	747
Lys Asp Gly Val Val	Thr Ile Glu	Glu Phe	Glu Ser Cys Gln Lys	
190	195	200	205	

gat gag aac atc atg agg tcc atg cag ctc ttt gac aat gtc atc 792
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<210> 26
<211> 220
<212> PRT
<213> Simian sp.

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      20          25          30

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Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
 35 40 45

Gln Thr Lys Phe Thr Arg Lys Glu Leu Gln Val Leu Tyr Arg Gly Phe
 50 55 60

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
 65 70 75 80

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Thr Tyr Ala Thr
 85 90 95

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
 100 105 110

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Val Asp
 115 120 125

Asp Arg Leu Asn Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
 130 135 140

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
 145 150 155 160

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
 165 170 175

Glu His Val Glu Asn Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
 180 185 190

Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn
 195 200 205

Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val Ile
 210 215 220

<210> 27

<211> 2057

<212> DNA

<213> Simian sp.

<220>

<221> CDS

<222> (208)..(963)

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ggccgcaggg ggcgcgtgtt gagccgccta ttctggccac ccggccgc 180

ccaggccggga gcggggcgcc gggggcc atg cgg ggc caa ggc aga aag gag agt 234
 Met Arg Gly Gln Gly Arg Lys Glu Ser

1

5

ttg tcc gaa tcc cga gat ctg gac ggc tcc tat gac cag ctt acg ggc 282
 Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
 10 15 20 25

07072360 * 95/02/2960

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His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys			
30	35	40	
ctg ctg ccg tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac	378		
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn			
45	50	55	
agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag	426		
Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu			
60	65	70	
ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg	474		
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu			
75	80	85	
cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc	522		
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val			
90	95	100	105
aac gag gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga	570		
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly			
110	115	120	
gac tcc agc aac tat gct act ttt ctc ttc aat gcc ttt gac acc aac	618		
Asp Ser Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn			
125	130	135	
cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tcg gtg	666		
His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val			
140	145	150	
att ctt ccg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta	714		
Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu			
155	160	165	
tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac	762		
Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp			
170	175	180	185
att atg aag tcc atc tat gac atg atg ggc aag tac aca tac ctc gcc	810		
Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala			
190	195	200	
ctc ccg gag gac gcc cca aga gaa cac gtg gag agc ttc ttc cag aag	858		
Leu Arg Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys			
205	210	215	
atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag	906		
Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu			
220	225	230	
tct tgt caa cag gag aac atc atg agg tcc atg cag ctc tca ccc	954		
Ser Cys Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Ser Pro			
235	240	245	
ctt ctc aac tgatacctag tgctgaggac accccctgggt tagggaccaa	1003		
Leu Leu Asn			
250			

0807260-952560

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 <212> PRT
 <213> Simian sp.

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 Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
 35 40 45
 Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
 50 55 60
 Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
 65 70 75 80
 Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
 85 90 95

USPTO-2004-09267-B10

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
 100 105 110

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr Ala Thr
 115 120 125

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
 130 135 140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Ile Asp
 145 150 155 160

Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
 165 170 175

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
 180 185 190

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Ala Pro Arg
 195 200 205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
 210 215 220

Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp Glu Asn
 225 230 235 240

Ile Met Arg Ser Met Gln Leu Ser Pro Leu Leu Asn
 245 250

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 <211> 1904
 <212> DNA
 <213> Rattus sp.

<220>
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 <222> (1)..(675)

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cga tct ctc tac cag ttg gta act ggg tcg ctg tcg cca gac agc gta
 Arg Ser Leu Tyr Gln Leu Val Thr Gly Ser Leu Ser Pro Asp Ser Val
 20 25 30

gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag ggc ctg
 Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
 35 40 45

gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg cag gtc
 Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
 50 55 60

ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc aac gag
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 65 70 75 80

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<210> 30
<211> 225
<212> PRT
<213> *Battus* sp.

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Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu
   35          40                   45

Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val
   50          55                   60

Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu
   65          70                   75                  80

Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gin Gly Asp Ser
   85          90                   95

Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp
  100         105                  110

Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu
  115         120                  125

Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp
  130         135                  140

Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met
  145         150                  155                  160

Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg
  165         170                  175

Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys Met Asp

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180	185	190
Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys		
195	200	205

Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Phe Asp Asn Val		
210	215	220

Ile
225

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<212> DNA
<213> Homo sapiens

<220>
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ggg gac ctc ggg cac aca cca ctt agc aag aag gag ggt atc aag tgg	96
Gly Asp Leu Gly His Thr Pro Leu Ser Lys Lys Glu Gly Ile Lys Trp	
20 25 30	

cag agg ccg agg ctc agc cgc cag gct ttg atg aga tgc tgc ctg gtc	144
Gln Arg Pro Arg Leu Ser Arg Gln Ala Leu Met Arg Cys Cys Leu Val	
35 40 45	

aag tgg atc ctg tcc agc aca gcc cca cag ggc tca gat agc agc gac	192
Lys Trp Ile Leu Ser Ser Thr Ala Pro Gln Gly Ser Asp Ser Ser Asp	
50 55 60	

agt gag ctg gag ctg tcc acg gtg cgc cac cag cca gag ggg ctg gac	240
Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp	
65 70 75 80	

cag ctg cag gcc cag acc aag ttc acc aag aag gag ctg cag tct ctc	288
Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu	
85 90 95	

tac agg ggc ttt aag aat gag tgt ccc acg ggc ctg gtg gac gaa gac	336
Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp	
100 105 110	

acc ttc aaa ctc att tac gcg cag ttc ttc cct cag gga gat gcc acc	384
Thr Phe Lys Leu Ile Tyr Ala Gln Phe Phe Pro Gln Gly Asp Ala Thr	
115 120 125	

acc tat gca cac ttc ctc ttc aac gcc ttt gat ggc gac ggg aac ggg	432
Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly	
130 135 140	

gcc atc cac ttt gag gac ttt gtg gtt ggc ctc tcc atc ctg ctg cgg	480
Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg	
145 150 155 160	

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Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
165 170 175

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Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys
180 185 190

tcc atc tat gac atg atg ggc cgc cac acc tac ccc atc ctg cgg gag 624
Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
195 200 205

gac gcg ccg gcg gag cac gtg gag agg ttc ttc gag aaa atg gac cgg 672
Asp Ala Pro Ala Glu His Val Glu Arg Phe Phe Glu Lys Met Asp Arg
210 215 220

aac cag gat ggg gta gtg acc att gaa gag ttc ctg gag gcc tgt cag 720
Asn Gln Asp Gly Val Val Thr Ile Glu Glu Phe Leu Glu Ala Cys Gln
225 230 235 240

aag gat gag aac atc atg agc tcc atg cag ctg ctt gag aat gtc atc 768
Lys Asp Glu Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
245 250 255

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<213> Homo sapiens

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1 5 10 15
Gly Asp Leu Gly His Thr Pro Leu Ser Lys Lys Glu Gly Ile Lys Trp
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Gln Arg Pro Arg Leu Ser Arg Gln Ala Leu Met Arg Cys Cys Leu Val
35 40 45
Lys Trp Ile Leu Ser Ser Thr Ala Pro Gln Gly Ser Asp Ser Ser Asp
50 55 60
Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp
65 70 75 80
Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu
85 90 95
Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
100 105 110

00/2360 95/07/960

Thr Phe Lys Leu Ile Tyr Ala Gln Phe Phe Pro Gln Gly Asp Ala Thr
 115 120 125

Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly
 130 135 140

Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg
 145 150 155 160

Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
 165 170 175

Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys
 180 185 190

Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
 195 200 205

Asp Ala Pro Ala Glu His Val Glu Arg Phe Phe Glu Lys Met Asp Arg
 210 215 220

Asn Gln Asp Gly Val Val Thr Ile Glu Glu Phe Leu Glu Ala Cys Gln
 225 230 235 240

Lys Asp Glu Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
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<210> 33
 <211> 442
 <212> DNA
 <213> Rattus sp.

<220>
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<400> 33
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 Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val
 1 5 10 15

cat gag aag ctc aag tgg gcc ttc aat ctc tac gac atc aac aag gac 96
 His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
 20 25 30

ggt tac atc acc aaa gag gag atg ctg gcc atc atg aag tcc atc tac 144
 Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
 35 40 45

gac atg atg ggc cgc cac acc tac cct atc ctg cgg gag gac gca cct 192
 Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
 50 55 60

ctg gag cat gtg gag agg ttc ttc cag aaa atg gac agg aac gag gat 240
 Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp
 65 70 75 80

gga gta gtg act att gat gaa ttt ctg gag act tgt cag aag gac gag 288

Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu
 85 90 95

aac atc atg agc tcc atg cag ctg ttt gag aac gtc atc taggacatgt 337
 Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
 100 105

aggagggggc cctgggtggc catgggtct caacccagag aagcctcaat cctgacagga 397

gaagcctcta tgagaaacat ttttctaata tatttgcaaa aagtg 442

<210> 34
<211> 109
<212> PRT
<213> Rattus sp.

<400> 34
Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val
 1 5 10 15

His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp
 20 25 30

Gly Tyr Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr
 35 40 45

Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro
 50 55 60

Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp
 65 70 75 80

Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu
 85 90 95

Asn Ile Met Ser Ser Met Gln Leu Phe Glu Asn Val Ile
 100 105

<210> 35
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<212> DNA
<213> Mus musculus

<220>
<221> CDS
<222> (49)..(816)

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Met Gln Arg
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acc aag gaa gcc gtg aag gca tca gat ggc aac ctc ctg gga gat cct 105
Thr Lys Glu Ala Val Lys Ala Ser Asp Gly Asn Leu Leu Gly Asp Pro
 5 10 15

ggg cgc ata cca ctg agc aag agg gaa agc atc aag tgg caa agg cca 153
Gly Arg Ile Pro Leu Ser Lys Arg Glu Ser Ile Lys Trp Gln Arg Pro
 20 25 30 35

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cgg ttc acc cgc cag gcc ctg atg cgt tgc tgc tta atc aag tgg atc	201
Arg Phe Thr Arg Gln Ala Leu Met Arg Cys Cys Leu Ile Lys Trp Ile	
40	45
50	
ctg tcc agt gct gcc cca caa ggc tca gag agc agt gac agt gaa ctg	249
Leu Ser Ser Ala Ala Pro Gln Gly Ser Asp Ser Asp Ser Glu Leu	
55	60
65	
gag tta tcc acg gtg cgc cat cag cca gag ggc ttg gac cag cta caa	297
Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp Gln Leu Gln	
70	75
80	
gct cag acc aag ttc acc aag aag gag ctg cag tcc ctt tac cga ggc	345
Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu Tyr Arg Gly	
85	90
95	
ttc aag aat gag tgt ccc aca ggc ctg gtg gat gaa gac acc ttc aaa	393
Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp Thr Phe Lys	
100	105
110	115
ctc att tat tcc cag ttc ttc cct cag gga gat gcc acc acc tat gca	441
Leu Ile Tyr Ser Gln Phe Pro Gln Gly Asp Ala Thr Thr Tyr Ala	
120	125
130	
cac ttc ctc ttc aat gcc ttt gat gct gat ggg aac ggg gcc acc tac cac	489
His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly Ala Ile His	
135	140
145	
ttt gag gac ttt gtg gtt ggg ctc tcc atc ctg ctt cga ggg acg gtc	537
Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg Gly Thr Val	
150	155
160	
cat gag aag ctc aag tgg gcc ttc aat ctc tat gac att aac aag gat	585
His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp	
165	170
175	
ggt tgc atc acc aag gag gag atg ctg gcc atc atg aag tcc atc tac	633
Gly Cys Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys Ser Ile Tyr	
180	185
190	195
gac atg atg ggc cgc cac acc tac ccc atc ctg cgg gag gat gca ccc	681
Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu Asp Ala Pro	
200	205
210	
ctg gag cat gtg gag agg ttc ttt cag aaa atg gac agg aac cag gat	729
Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg Asn Gln Asp	
215	220
225	
gga gtg gtg acc att gat gaa ttt ctg gag act tgt gag aag gat gag	777
Gly Val Val Thr Ile Asp Glu Phe Leu Glu Thr Cys Gln Lys Asp Glu	
230	235
240	
aac atc atg aac tcc atg cag ctg ttt gag aac gtc atc taggacatgt	826
Asn Ile Met Asn Ser Met Gln Leu Phe Glu Asn Val Ile	
245	250
255	
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aagctcttat gagaacattttctataat atttgaaaaa agtgagcagt ttacttccaa 946	

gacacagcca ccgtcacaca cagacacaga catacagaca cacacacaca cacacacaca 1006
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tcccttagcc tctgggtcGA CGCCCAACCT GGAGGGGTCT GTCCCTTTG CAGGGACACA 2506
gactggccgc atgtccgcAT GGCAGAAGCG TCTCCCTTG GTGCAGCCTG GAAGGGTGT 2566
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aggaaaaaaaaaaaaaaa 2644

<210> 36
<211> 256

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<212> PRT

<213> Mus musculus

<400> 36

Gly Asp Pro Gly Arg Ile Pro Leu Ser Lys Arg Glu Ser Ile Lys Trp
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Gln Arg Pro Arg Phe Thr Arg Gln Ala Leu Met Arg Cys Cys Leu Ile
35 40 45

Lys Trp Ile Leu Ser Ser Ala Ala Pro Gln Gly Ser Asp Ser Ser Asp
50 55 60

Ser Glu Leu Glu Leu Ser Thr Val Arg His Gln Pro Glu Gly Leu Asp
65 70 75 80

Gln Leu Gln Ala Gln Thr Lys Phe Thr Lys Lys Glu Leu Gln Ser Leu
85 90 95

Tyr Arg Gly Phe Lys Asn Glu Cys Pro Thr Gly Leu Val Asp Glu Asp
100 105 110

Thr Phe Lys Leu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ala Thr
115 120 125

Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Ala Asp Gly Asn Gly
130 135 140

Ala Ile His Phe Glu Asp Phe Val Val Gly Leu Ser Ile Leu Leu Arg
145 150 155 160

Gly Thr Val His Glu Lys Leu Lys Trp Ala Phe Asn Leu Tyr Asp Ile
165 170 175

Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Ala Ile Met Lys
180 185 190

Ser Ile Tyr Asp Met Met Gly Arg His Thr Tyr Pro Ile Leu Arg Glu
195 200 205

Asp Ala Pro Leu Glu His Val Glu Arg Phe Phe Gln Lys Met Asp Arg
210 215 220

Asn	Gln	Asp	Gly	Val	Val	Thr	Ile	Asp	Glu	Phe	Leu	Glu	Thr	Cys	Gln
225				230					235					240	

Lys Asp Glu Asn Ile Met Asn Ser Met Gln Leu Phe Glu Asn Val Ile
245 250 255

<210> 37

<212> BNP

卷之三

<220>

222

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<220>

<223> At position 495, n=any amino acid

<400> 37

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His Glu Val Glu Ser Ile Ser Ala Gln Leu Glu Glu Ala Ser Ser Thr
   1         5          10        15

```

```

ggc ggt ttc ctg tac gct cag aac agc acc aag cgc agc att aaa gag 96
Gly Gly Leu Tyr Phe Ala Gln Asn Ser Thr Lys Arg Ser Ile Lys Glu
          20           25           30

```

```

cggttcatggcttgcgtttcaacggccaaatcgatcgtttcc 144
Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr Ser Ser Pro
      35          40          45

```

```

gct att caa aac agc gtg gaa gat gaa ctg gag atg gcc acc gtc agg 192
Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg
      50           55           60

```

```

cat cgg ccc gaa gcc ctt gag ctt ctg gaa gcc cag agc aaa ttt acc 240
His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr
       65          70           75           80

```

```

aag aaa gag ctt caa atc ctt tac aga gga ttt aag aac gta aga act  288
Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Val Arg Thr
          85           90           95

```

```

ttc ttt ttg act tta cct tca cac aat tcc cag agg agc att gag aaa 336
Phe Phe Leu Thr Leu Pro Ser His Asn Ser Gln Arg Ser Ile Glu Lys
          100      105      110

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tgagaggaaa agggggaaaa tatccatc tatgagaagc cccatcatat gtatattca 396
tactgtatcc tccccatcgat gaataataatc agtatctgtg gactttgaat ctctgtggca 456

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caccatgtt ggcatactgt aattccccat taaacaaana gtttttgaga aaaaaaaaaa 516  
aaaaaaaaaa aaaaaa 531
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<210> 38

<211> 112

<212> PRT

<213> Homo sapiens

<400> 38

Gly Gly Phe Leu Tyr Ala Gln Asn Ser Thr Lys Arg Ser Ile Lys Glu
 20 25 30

Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr Ser Ser Pro
35 40 45

Ala Ile Gin Asn Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg
50 55 60

His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr
65 70 75 80

Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Val Arg Thr
85 90 95

Phe Phe Leu Thr Leu Pro Ser His Asn Ser Gln Arg Ser Ile Glu Lys
100 105 110

<210> 39
<211> 2176
<212> DNA
<213> *Homo sapien*

<220>
<221> CDS
<222> (?) -- (124)

<400> 39

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t gaa agg ttc ttc gag aaa atg gac cgg aac cag gat ggg gta gtg acc 49
  Glu Arg Phe Phe Glu Lys Met Asp Arg Asn Gln Asp Gly Val Val Thr
   1          5           10          15

```

```

att gaa gag ttc ctg gag gcc tgt cag aag gat gag aac atc atg agc 97
Ile Glu Glu Phe Leu Glu Ala Cys Gln Lys Asp Glu Asn Ile Met Ser
 20      25      30

```

tcc atg cag ctg ttt gagaatgtc atc taggacacgt ccaaaggagt 144
Ser Met Gln Leu Phe Glu Asn Val Ile
35 40

gcatggccac agccacacctcc accccccaaaga aacctccatc ctgccaggag cagcctccaa 204

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ggggggggggggc gagccggggcc agggggggggag cccaggagggc ccagccggcc cccccccgggc 384

ooooooooooooo oooooooaaaaaaag oooooooaaaaaaag oooooooaaaaaaag oooooooaaaaaaag oooooooaaaaaaag oooooooaaaaaaag oooooooaaaaaaag

9999999999 9999999999 9999999999 9999999999 9999999999 9999999999 9999999999 999

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tctcccttgg ccacggccctg ggaggggtgg tcttgttctc agcattccact aatattcagt 2124
cctgtatatt ttaataaaat aaacttgaca aaaaaaaaaaaaaaa aa 2176

<210> 40
<211> 41
<212> PRT
<213> Homo sapiens

<400> 40
Glu Arg Phe Phe Glu Lys Met Asp Arg Asn Gln Asp Gly Val Val Thr
1 5 10 15

Ile Glu Glu Phe Leu Glu Ala Cys Gln Lys Asp Glu Asn Ile Met Ser
20 25 30

Ser Met Gln Leu Phe Glu Asn Val Ile
35 40

<210> 41
<211> 2057
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (208)..(963)

<400> 41
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tctctaaaga aaaggcttc cagccctac tccggcccc caaccccagc aggtcgctgc 120
ggcccccaggc ggccgtgtgt gagccctta ttctggccac ccggccccc ctcccacggc 180
ccaggcggga gcggggcgcc gggggcc atg cgg ggc caa ggc aga aag gag agt 234
Met Arg Gly Gln Gly Arg Lys Glu Ser
 1 5
ttg tcc gaa tcc cga gat ctg gac ggc tcc tat gac cag ctt acg ggc 282
Leu Ser Glu Ser Arg Asp Leu Asp Gly Ser Tyr Asp Gln Leu Thr Gly
10 15 20 25
cac cct cca ggg ccc agt aaa aaa gcc ctg aag cag cgt ttc ctc aag 330
His Pro Pro Gly Pro Ser Lys Lys Ala Leu Lys Gln Arg Phe Leu Lys
 30 35 40
ctg ctg ccc tgc tgc ggg ccc caa gcc ctg ccc tca gtc agt gaa aac 378
Leu Leu Pro Cys Cys Gly Pro Gln Ala Leu Pro Ser Val Ser Glu Asn
 45 50 55
agc gta gag gat gag ttt gaa tta tcc acg gtg tgt cac cga cct gag 426
Ser Val Glu Asp Glu Phe Glu Leu Ser Thr Val Cys His Arg Pro Glu
 60 65 70
ggc ctg gaa caa ctc cag gaa cag acc aag ttc aca cgc aga gag ctg 474
Gly Leu Glu Gln Leu Gln Glu Gln Thr Lys Phe Thr Arg Arg Glu Leu
 75 80 85
cag gtc ctg tac cga ggc ttc aag aac gaa tgc ccc agt ggg att gtc 522
Gln Val Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Ile Val
 90 95 100 105
aac gag gag aac ttc aag cag att tat tct cag ttc ttt ccc caa gga 570
Asn Glu Glu Asn Phe Lys Gln Ile Tyr Ser Gln Phe Phe Pro Gln Gly
 110 115 120
gac tcc agc aac tat gtc act ttt ctc ttc aat gcc ttt gac acc aac 618
Asp Ser Ser Asn Tyr Ala Thr Phe Leu Phe Asn Ala Phe Asp Thr Asn
 125 130 135
cac gat ggc tct gtc agt ttt gag gac ttt gtg gct ggt ttg tcg gtg 666
His Asp Gly Ser Val Ser Phe Glu Asp Phe Val Ala Gly Leu Ser Val
 140 145 150
att ctt cgg ggg acc ata gat gat aga ctg agc tgg gct ttc aac tta 714
Ile Leu Arg Gly Thr Ile Asp Asp Arg Leu Ser Trp Ala Phe Asn Leu
 155 160 165
tat gac ctc aac aag gac ggc tgt atc aca aag gag gaa atg ctt gac 762
Tyr Asp Leu Asn Lys Asp Gly Cys Ile Thr Lys Glu Glu Met Leu Asp
170 175 180 185
att atg aag tcc atc tat gac atg ggc aag tac aca tac cct gcc 810
Ile Met Lys Ser Ile Tyr Asp Met Met Gly Lys Tyr Thr Tyr Pro Ala

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190	195	200	
ctc cgg gag gag gcc cca aga gaa cac gtg gag agc ttc ttc cag aag Leu Arg Glu Glu Ala Pro Arg Glu His Val Glu Ser Phe Phe Gln Lys 205	210	215	858
atg gac agg aac aag gac ggc gtg gtg acc atc gag gaa ttc atc gag Met Asp Arg Asn Lys Asp Gly Val Val Thr Ile Glu Glu Phe Ile Glu 220	225	230	906
tct tgt caa cag gag aac atc atg agg tcc atg cag ctc tca ccc Ser Cys Gln Gln Asp Glu Asn Ile Met Arg Ser Met Gln Leu Ser Pro 235	240	245	954
ctt ctc aac tgatacctag tgctgaggac acccctggtg tagggaccaa Leu Leu Asn 250			1003
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<210> 42
<211> 252
<212> PRT
<213> Rattus sp.

<400> 42

00022600-00259-00000

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Asp Gly Ser Tyr Asp Gln Leu Thr Gly His Pro Pro Gly Pro Ser Lys
20 25 30

Lys Ala Leu Lys Gln Arg Phe Leu Lys Leu Leu Pro Cys Cys Gly Pro
35 40 45

Gln Ala Leu Pro Ser Val Ser Glu Asn Ser Val Glu Asp Glu Phe Glu
50 55 60

Leu Ser Thr Val Cys His Arg Pro Glu Gly Leu Glu Gln Leu Gln Glu
65 70 75 80

Gln Thr Lys Phe Thr Arg Arg Glu Leu Gln Val Leu Tyr Arg Gly Phe
85 90 95

Lys Asn Glu Cys Pro Ser Gly Ile Val Asn Glu Glu Asn Phe Lys Gln
100 105 110

Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Ser Asn Tyr Ala Thr
115 120 125

Phe Leu Phe Asn Ala Phe Asp Thr Asn His Asp Gly Ser Val Ser Phe
130 135 140

Glu Asp Phe Val Ala Gly Leu Ser Val Ile Leu Arg Gly Thr Ile Asp
145 150 155 160

Asp Arg Leu Ser Trp Ala Phe Asn Leu Tyr Asp Leu Asn Lys Asp Gly
165 170 175

Cys Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ser Ile Tyr Asp
180 185 190

Met Met Gly Lys Tyr Thr Tyr Pro Ala Leu Arg Glu Glu Ala Pro Arg
195 200 205

Glu His Val Glu Ser Phe Phe Gln Lys Met Asp Arg Asn Lys Asp Gly
210 215 220

Val Val Thr Ile Glu Glu Phe Ile Glu Ser Cys Gln Gln Asp Glu Asn
225 230 235 240

Ile Met Arg Ser Met Gln Leu Ser Pro Leu Leu Asn
245 250

<210> 43

<211> 26

<212> PRT

<213> Artificial Sequence

<220>

<223> Xaas at positions 2,5,6,9,17,25 and 26 may be Ile,
Leu, Val or Met

<220>

<223> Xaas at positions 3,4,7,8,16,18-20,23 and 24 may
be any amino acid

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<220>
<223> Description of Artificial Sequence: consensus
motif

<400> 43
Glu Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asp Lys Asp Gly Asp Gly Xaa
1 5 10 15

Xaa Xaa Xaa Xaa Glu Phe Xaa Xaa Xaa Xaa
20 25

<210> 44
<211> 40
<212> DNA
<213> Rattus sp.

<400> 44
taatacgact cactataggg actggccatc ctgtctcaag

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<210> 45
<211> 40
<212> DNA
<213> Rattus sp.

<400> 45
attaaccctc actaaaggga cactactgtt taagctcaag

40

<210> 46
<211> 40
<212> DNA
<213> Rattus sp.

<400> 46
taatacgact cactataggg cacctccccct ccggctgttc

40

<210> 47
<211> 40
<212> DNA
<213> Rattus sp.

<400> 47
attaaccctc actaaaggga gagcagcagc atggcagggt

40

<210> 48
<211> 2413
<212> DNA
<213> Simian sp.

<220>
<221> CDS
<222> (265)..(963)

<400> 48
gtcgaccac gctgcccgtg cgctgtggtt gcggggggga gccccgccag ccaaatgcca 60

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ggatcagcat gagaggctgg acttttagtc aggtctgtc tcaccccggy ggaccgcgg 120
 ctttgcaggg tgcagctgctc aggaactgct cactttttc cccttgcaag tctttgttcc 180
 aagcctgacg ttgctacat tctgttaatta actccctcca ctccaaagg gtctggaggc 240
 tggatgctc tgccagctca gagg atg ttg act ctg gag tgg gag tcc gaa 291
 Met Leu Thr Leu Glu Trp Glu Ser Glu
 1 5

gga ctg caa aca gtg ggt att gtt gtg att ata tgt gca tct ctg aag 339
 Gly Leu Gln Thr Val Gly Ile Val Val Ile Cys Ala Ser Leu Lys
 10 15 20 25

ctg ctt cat ttg ctg gga ctg att gat ttt tcg gaa gac agc gtg gaa 387
 Leu Leu His Leu Leu Gly Ile Asp Phe Ser Glu Asp Ser Val Glu
 30 35 40

gat gaa ctg gag atg gcc act gtc agg cat cgg cct gag gcc ctt gag 435
 Asp Glu Leu Glu Met Ala Thr Val Arg His Arg Pro Glu Ala Leu Glu
 45 50 55

ctt ctg gaa gcc cag agc aaa ttt acc aag aaa gag ctt cag atc ctt 483
 Leu Leu Glu Ala Gln Ser Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu
 60 65 70

tac aga gga ttt aag aac gaa tgc ccc agt ggt gtt gtt aat gaa gaa 531
 Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val Asn Glu Glu
 75 80 85

acc ttc aaa gag att tac tcg cag ttc ttt cca cag gga gac tct aca 579
 Thr Phe Lys Glu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr
 90 95 100 105

aca tat gca cat ttt ctg ttc aat gcg ttt gat acg gac cac aat gga 627
 Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Thr Asp His Asn Gly
 110 115 120

gct gtg agt ttc gag gat ttc atc aaa ggt ctt tcc att ttg ctc cgg 675
 Ala Val Ser Phe Glu Asp Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg
 125 130 135

ggg aca gta caa gaa aaa ctc aat tgg gca ttt aat ctg tat gat ata 723
 Gly Thr Val Gln Glu Lys Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile
 140 145 150

aat aaa gat ggc tac atc act aaa gag gaa atg ctt gat ata atg aaa 771
 Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys
 155 160 165

gca ata tac gac atg atg ggt aaa tgt aca tat cct gtc ctc aaa gaa 819
 Ala Ile Tyr Asp Met Met Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu
 170 175 180 185

gat gca ccc aga caa cac gtc gaa aca ttt ttt cag aaa atg gac aaa 867
 Asp Ala Pro Arg Gln His Val Glu Thr Phe Phe Gln Lys Met Asp Lys
 190 195 200

aat aaa gat ggg gtt gtt acc ata gat gag ttc att gaa agc tgc caa 915
 Asn Lys Asp Gly Val Val Thr Ile Asp Glu Phe Ile Glu Ser Cys Gln
 205 210 215

<210> 49
<211> 233
<212> PRT
<213> Simian sp.

<400> 49
Met Leu Thr Leu Glu Trp Glu Ser Glu Gly Leu Gln Thr Val Gly Ile
1 5 10 15

Val Val Ile Ile Cys Ala Ser Leu Lys Leu Leu His Leu Leu Gly Leu
20 25 30

Ile Asp Phe Ser Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr
35 40 45

Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys
50 55 60

Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Glu
65 70 75 80

Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr Ser
85 90 95

Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu Phe
100 105 110

Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp Phe
115 120 125

Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys Leu
130 135 140

Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Thr
145 150 155 160

Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met Gly
165 170 175

Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His Val
180 185 190

Glu Thr Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val Thr
195 200 205

Ile Asp Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met Arg
210 215 220

Ser Met Gln Leu Phe Glu Asn Val Ile
225 230

<210> 50

<211> 1591

<212> DNA

<213> Simian sp.

<220>

<221> CDS

<222> (265)..(963)

<400> 50

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ggatcagcat gagaggctgg acttttagtcc aggtctgtcc tcaccccggg ggaccggccgg 120

ctttcaggg tgcagctgca aggaactgct cactttttc cccttgcagg tctttgtcc 180
 aagcctgacg ttgctacat tctgtatattt actccctcca ctccaaagggt gtctggggc 240
 tggatgctc tgccagctca gagg atg ttg act ctg gag tgg gag tcc gaa 291
 Met Leu Thr Leu Glu Trp Glu Ser Glu
 1 5
 gga ctg caa aca gtt ggt att gtt gtt att ata tgt gca tct ctg aag 339
 Gly Leu Gln Thr Val Gly Ile Val Val Ile Ile Cys Ala Ser Leu Lys
 10 15 20 25
 ctg ctt cat ttg ctg gga ctg att gat ttt tcg gaa gac agc gtg gaa 387
 Leu Leu His Leu Leu Gly Ile Asp Phe Ser Glu Asp Ser Val Glu
 30 35 40
 gat gaa ctg gag atg gcc act gtc agg cat cgg cct gag gcc ctt gag 435
 Asp Glu Leu Glu Met Ala Thr Val Arg His Arg Pro Glu Ala Leu Glu
 45 50 55
 ctt ctg gaa gcc cag aac aaa ttt acc aag aaa gag ctt cag atc ctt 483
 Leu Leu Glu Ala Gln Ser Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu
 60 65 70
 tac aga gga ttt aag aac gaa tgc ccc agt ggt gtt gtt aat gaa gaa 531
 Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly Val Val Asn Glu Glu
 75 80 85
 acc ttc aaa gag att tac tgc cag ttc ttt cca cag gga gac tct aca 579
 Thr Phe Lys Glu Ile Tyr Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr
 90 95 100 105
 aca tat gca cat ttt ctg ttc aat gcg ttt gat acg gac cac aat gga 627
 Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp Thr Asp His Asn Gly
 110 115 120
 gct gtg agt ttc gag gat ttc atc aaa ggt ctt tcc att ttg ctc cgg 675
 Ala Val Ser Phe Glu Asp Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg
 125 130 135
 ggg aca gta caa gaa aaa ctc aat tgg gca ttt aat ctg tat gat ata 723
 Gly Thr Val Gln Glu Lys Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile
 140 145 150
 aat aaa gat ggc tac atc act aaa gag gaa atg ctt gat ata atg aaa 771
 Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met Leu Asp Ile Met Lys
 155 160 165
 gca ata tac gac atg atg ggt aaa tgt aca tat cct gtc ctc aaa gaa 819
 Ala Ile Tyr Asp Met Met Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu
 170 175 180 185
 gat gca ccc aga caa cac gtc gaa aca ttt ttt cag gct gtt ttc cat 867
 Asp Ala Pro Arg Gln His Val Glu Thr Phe Phe Gln Ala Val Phe His
 190 195 200
 tgt atc atc aag tgg aag ttc aag acg gca tca aac aaa aca agg atg 915
 Cys Ile Ile Lys Trp Lys Phe Lys Thr Ala Ser Asn Lys Thr Arg Met
 205 210 215

00026095202960

ttt aca gac ata tgc aaa ggg tca gga tat cta tcc tcc agt ata tgt 963
 Phe Thr Asp Ile Cys Lys Gly Ser Gly Tyr Leu Ser Ser Ile Cys
 220 225 230

taatgcttaa taacaagtaa tcctaacagc attaaaggcc aaatctgtcc tctttccct 1023
 gacttcctta cagcatgttt atattacaag ccattcaggg acaaagaaac cttagactacc 1083
 ccactgtcta ctaggaacaa acaaacagca agcaaattc actttgaaag caccagtgg 1143
 tccattacat tgacaactac taccaagatt cagtagaaaa taatgtctca acaactaatac 1203
 cagattacaa tatgattna tgcatcataa aattccaaca attcagatta tttttatca 1263
 tctcagccac aactgttaag ttgccacatt actaaagaca cacacatcg ccctgtttt 1323
 tagaaatatac acaaagacca agaggctaca gaaggaggaa atttgcaact gtcttgcaa 1383
 caataaaatca ggtatctatt ctggtgtaga gataggatgt taaaagctgc cctgctatca 1443
 ccagtgtaga aatthaagagt agtacaatac atgtacactg aaatttgccaa tcgcgtgtt 1503
 gtgtaaactc aatgtgcaca ttttgtatt caaaaagaaa aaataaaagc aaaataaaat 1563
 gttwawaamw mwaaaaaaaaaaaaaaa 1591

<210> 51
<211> 233
<212> PRT
<213> Simian sp.

<400> 51
Met Leu Thr Leu Glu Trp Glu Ser Glu Gly Leu Gln Thr Val Gly Ile
 1 5 10 15

Val Val Ile Ile Cys Ala Ser Leu Lys Leu Leu His Leu Leu Gly Leu
 20 25 30

Ile Asp Phe Ser Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr
 35 40 45

Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys
 50 55 60

Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Glu
 65 70 75 80

Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr Ser
 85 90 95

Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu Phe
 100 105 110

Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp Phe
 115 120 125

Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys Leu
 130 135 140

Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Thr

001/2360-95/0/950

145	150	155	160
Lys Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met Gly			
165	170	175	
Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His Val			
180	185	190	
Glu Thr Phe Phe Gln Ala Val Phe His Cys Ile Ile Lys Trp Lys Phe			
195	200	205	
Lys Thr Ala Ser Asn Lys Thr Arg Met Phe Thr Asp Ile Cys Lys Gly			
210	215	220	
Ser Gly Tyr Leu Ser Ser Ser Ile Cys			
225	230		

<210> 52
<211> 2051
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (85)..(1305)

<400> 52
ggtggagcta agcactca ctgcgtgtgc cctgcgtctg cagagaacaa ggaaggcttc 60

tctgcaggcc tgcgtgtgc caaaa atg aac ggc gtg gaa ggg aac aac gag 111
Met Asn Gly Val Gly Asn Asn Glu
1 5

ctc ctc ctc gct aac acc tcg acc tcc gcc ctt gtc ccg gaa gat ctg 159
Leu Pro Leu Ala Asn Thr Ser Thr Ala Leu Val Pro Glu Asp Leu
10 15 20 25

gat ctg aag caa gac cag ccg ctc agc gag gaa act gac acg gtg cgg 207
Asp Leu Lys Gln Asp Gln Pro Leu Ser Glu Glu Thr Asp Thr Val Arg
30 35 40

gag atg gag gct gca ggt gag gcc ggt gcg gag gga ggc ggc tcc ccc 255
Glu Met Glu Ala Ala Gly Glu Ala Gly Ala Glu Gly Gly Ala Ser Pro
45 50 55

gat tcg gag cac tgc gac ccc cag ctc tgc ctc cga gtg gct gag aat 303
Asp Ser Glu His Cys Asp Pro Gln Leu Cys Leu Arg Val Ala Glu Asn
60 65 70

ggc tgt gct gcc gca gcg gga gag ggg ctg gag gat ggt ctg tct tca 351
Gly Cys Ala Ala Ala Gly Glu Gly Leu Glu Asp Gly Leu Ser Ser
75 80 85

tca aag tgt ggg gac gca ccc ttg gcg tct gtg gca gcc aac gac agc 399
Ser Lys Cys Gly Asp Ala Pro Leu Ala Ser Val Ala Ala Asn Asp Ser
90 95 100 105

aat aaa aat ggc tgt cag ctt gca ggg ccg ctc agc cct gct aag cca 447
Asn Lys Asn Gly Cys Gln Leu Ala Gly Pro Leu Ser Pro Ala Lys Pro
110 115 120

01022365/95/05/29950

aaa act ctg gaa gcc agt ggt gca gtg ggc ctg ggg tcg cag atg atg 495
 Lys Thr Leu Glu Ala Ser Gly Ala Val Gly Leu Gly Ser Gln Met Met
 125 130 135

 cca ggg ccg aag aag acc aag gta atg act acc aag ggc gcc atc tct 543
 Pro Gly Pro Lys Lys Thr Lys Val Met Thr Thr Lys Gly Ala Ile Ser
 140 145 150

 gcg act aca ggc aag gaa gga gaa gca ggg gcg gca atg cag gaa aag 591
 Ala Thr Thr Gly Lys Glu Gly Glu Ala Gly Ala Ala Met Gln Glu Lys
 155 160 165

 aag ggg gtg cag aaa gaa aaa aag gca gct gga gga ggg aaa gac gag 639
 Lys Gly Val Gln Lys Glu Lys Ala Ala Gly Gly Lys Asp Glu
 170 175 180 185

 act cgt cct aga gcc cct aag atc aat aac tgc atg gac tcc ctg gaa 687
 Thr Arg Pro Arg Ala Pro Lys Ile Asn Asn Cys Met Asp Ser Leu Glu
 190 195 200

 gcc atc gat caa gag ctg tca aat gta aat gcg caa gct gac agg gcc 735
 Ala Ile Asp Gln Glu Leu Ser Asn Val Asn Ala Gln Ala Asp Arg Ala
 205 210 215

 ttc ctc cag ctg gaa cgc aaa ttt ggg cggt atg aga agg ctc cac atg 783
 Phe Leu Gln Leu Glu Arg Lys Phe Gly Arg Met Arg Arg Leu His Met
 220 225 230

 cag cgc cga agt ttc atc atc caa aac atc cca ggt ttc tgg gtc aca 831
 Gln Arg Arg Ser Phe Ile Ile Gln Asn Ile Pro Gly Phe Trp Val Thr
 235 240 245

 gcg ttt cgg aac cac ccg caa ctg tca ccg atg atc agt ggc caa gat 879
 Ala Phe Arg Asn His Pro Gln Leu Ser Pro Met Ile Ser Gly Gln Asp
 250 255 260 265

 gaa gac atg atg agg tac atg atc aat tta gag gtg gag gag ctt aag 927
 Glu Asp Met Met Arg Tyr Met Ile Asn Leu Glu Val Glu Glu Leu Lys
 270 275 280

 cac cca aga gca ggg tgc aaa ttt aag ttc atc ttc caa agc aac ccc 975
 His Pro Arg Ala Gly Cys Lys Phe Lys Phe Ile Phe Gln Ser Asn Pro
 285 290 295

 tac ttc cga aat gag ggg ctg gtc aaa gag tac gag cgc aga tcc tca 1023
 Tyr Phe Arg Asn Glu Gly Leu Val Lys Glu Tyr Glu Arg Arg Ser Ser
 300 305 310

 ggt cga gtg gtg tgc ctc tct acg cca atc ccg tgg cac cgg ggt caa 1071
 Gly Arg Val Val Ser Leu Ser Thr Pro Ile Arg Trp His Arg Gly Gln
 315 320 325

 gaa ccc cag gcc cat atc cac agg aat aga gag ggg aac acg att ccc 1119
 Glu Pro Gln Ala His Ile His Arg Asn Arg Glu Gly Asn Thr Ile Pro
 330 335 340 345

 agt ttc ttc aat tgg ttc tca gac cac agc ctc cta gaa ttc gac aga 1167
 Ser Phe Phe Asn Trp Phe Ser Asp His Ser Leu Leu Glu Phe Asp Arg
 350 355 360

0002260-0152/0250

ata gct gaa att atc aaa ggg gag ctt tgg tcc aat ccc cta caa tac	1215		
Ile Ala Glu Ile Ile Lys Gly Glu Leu Trp Ser Asn Pro Leu Gln Tyr			
365	370		375
	375		

tac ctg atg ggc gat ggg cca cgc aga gga gtt cga gtc cca cca agg	1263		
Tyr Leu Met Gly Asp Gly Pro Arg Arg Gly Val Arg Val Pro Pro Arg			
380	385		390
	390		

cag cca gtg gag agt ccc agg tcc ttc agg ttc cag tct ggc	1305		
Gln Pro Val Glu Ser Pro Arg Ser Phe Arg Phe Gln Ser Gly			
395	400		405
	405		

taagctctgc cctcgtgaga agctcttaca gaagagtccct taccaccc tcagcttggc	1365
--	------

tagcagcatg cagccttctg tctgtttctt cttccttggta ttgtgtccctt tggttcttct	1425
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aagtctcccg tagtttcaag gtttgtggctt ccaagttttt gctttttttt ctcttggcca	1485
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tcacatgttc ctgcataatg ttaatgggt tccaaatgtca tggcctccaa actgtttcta	1545
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tgccaaatgttc acgtgtgtta gtttgtactg cttttcttgcatggcttgg ttcctgtctg	1605
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tgtatcttctta ggttttttgt tttttttttt aaatgtgtt ctctatcaa agaaatgttgc	1665
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acatatccctt accaagaactt agccagattt catactgtgt tcccgatatac tatgtactgt	1725
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gaagaactgtt gagtttgcctt actgcaagat gggactgttat ccaatccag ccatcagccc	1785
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aacaggacat tccaaatgtt caccaactgtt cccttagtctgtt cttccttggc ctttgcatt	1845
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taccctgtttt ttatctataa gaatggggcgtt gttgtactactt aggttaagagt	1905
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gaagttttttttttagt gtgaggagttt ttttctgtca ccacattgtt cttgtaccaa tgcatacatgt	1965
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tcaatgttggaa tcaatgttactt actgttctgtat atttctaaacc cccaaacacaa aaaaaaaaaa	2025
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aaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa aaaaaaaaaaaaaaaa	2051
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<210> 53

<211> 407

<212> PRT

<213> Rattus sp.

<400> 53

Met Asn Gly Val Glu Gly Asn Asn Glu Leu Pro Leu Ala Asn Thr Ser					
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	10		15		
	15				

Thr Ser Ala Leu Val Pro Glu Asp Leu Asp Leu Lys Gln Asp Gln Pro			
20	25		30
	30		

Leu Ser Glu Glu Glu Thr Asp Thr Val Arg Glu Met Glu Ala Ala Gly Glu			
35	40		45
	45		

Ala Gly Ala Glu Gly Gly Ala Ser Pro Asp Ser Glu His Cys Asp Pro			
50	55		60
	60		

Gln Leu Cys Leu Arg Val Ala Glu Asn Gly Cys Ala Ala Ala Gly					
65	70		75		80
	75		80		
	80				

m2265-0527960

Glu Gly Leu Glu Asp Gly Leu Ser Ser Ser Lys Cys Gly Asp Ala Pro
85 90 95

Leu Ala Ser Val Ala Ala Asn Asp Ser Asn Lys Asn Gly Cys Gln Leu
100 105 110

Ala Gly Pro Leu Ser Pro Ala Lys Pro Lys Thr Leu Glu Ala Ser Gly
115 120 125

Ala Val Gly Leu Gly Ser Gln Met Met Pro Gly Pro Lys Lys Thr Lys
130 135 140

Val Met Thr Thr Lys Gly Ala Ile Ser Ala Thr Thr Gly Lys Glu Gly
145 150 155 160

Glu Ala Gly Ala Ala Met Gln Glu Lys Lys Gly Val Gln Lys Glu Lys
165 170 175

Lys Ala Ala Gly Gly Lys Asp Glu Thr Arg Pro Arg Ala Pro Lys
180 185 190

Ile Asn Asn Cys Met Asp Ser Leu Glu Ala Ile Asp Gln Glu Leu Ser
195 200 205

Asn Val Asn Ala Gln Ala Asp Arg Ala Phe Leu Gln Leu Glu Arg Lys
210 215 220

Phe Gly Arg Met Arg Arg Leu His Met Gln Arg Arg Ser Phe Ile Ile
225 230 235 240

Gln Asn Ile Pro Gly Phe Trp Val Thr Ala Phe Arg Asn His Pro Gln
245 250 255

Leu Ser Pro Met Ile Ser Gly Gln Asp Glu Asp Met Met Arg Tyr Met
260 265 270

Ile Asn Leu Glu Val Glu Glu Leu Lys His Pro Arg Ala Gly Cys Lys
275 280 285

Phe Lys Phe Ile Phe Gln Ser Asn Pro Tyr Phe Arg Asn Glu Gly Leu
290 295 300

Val Lys Glu Tyr Glu Arg Arg Ser Ser Gly Arg Val Val Ser Leu Ser
305 310 315 320

Thr Pro Ile Arg Trp His Arg Gly Gln Glu Pro Gln Ala His Ile His
325 330 335

Arg Asn Arg Glu Gly Asn Thr Ile Pro Ser Phe Phe Asn Trp Phe Ser
340 345 350

Asp His Ser Leu Leu Glu Phe Asp Arg Ile Ala Glu Ile Ile Lys Gly
355 360 365

Glu Leu Trp Ser Asn Pro Leu Gln Tyr Tyr Leu Met Gly Asp Gly Pro
370 375 380

Arg Arg Gly Val Arg Val Pro Pro Arg Gln Pro Val Glu Ser Pro Arg
385 390 395 400

Ser Phe Arg Phe Gln Ser Gly

DD/260-95/07950

405

<210> 54
<211> 4148
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (88)..(1329)

<400> 54
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tctcccacta gtctgacttc ttccaaa atg	agc	ggc	ctg	gat	ggg	ggc	aac	aag	114
Met	Ser	Gly	Leu	Asp	Gly	Gly	Asn	Lys	5
1									

ctc	cct	ctc	gcc	caa	acc	ggc	ggc	ctg	gct	gct	ccc	gac	cat	gcc	tca	162
Leu	Pro	Leu	Ala	Gln	Thr	Gly	Gly	Leu	Ala	Ala	Pro	Asp	His	Ala	Ser	25
10																

gga	aat	ccg	gac	cta	gac	cag	tgc	caa	ggg	ctc	cgt	gaa	gaa	acc	gag	210
Gly	Asp	Pro	Asp	Leu	Asp	Gln	Cys	Gin	Gly	Gly	Leu	Arg	Glu	Glu	Thr	Glu
30																

gcg	aca	cag	gtg	atg	gct	gct	gac	aca	ggt	ggg	ggc	agc	ctg	gag	acc	gtt	258
Ala	Thr	Gln	Val	Met	Ala	Asn	Thr	Gly	Gly	Gly	Gly	Ser	Leu	Glu	Thr	Val	
45																	

gcg	gag	ggg	ggt	gca	tcc	cag	gat	cct	gtc	gac	tgt	ggc	ccc	gctc	306
Ala	Glu	Gly	Gly	Ala	Ser	Gln	Asp	Pro	Val	Asp	Cys	Gly	Pro	Ala	Leu
60															

cgc	gtc	cca	gtt	gcc	ggg	agt	cgc	ggc	ggt	gca	gct	acc	aaa	gcc	ggg	354
Arg	Val	Pro	Val	Ala	Gly	Ser	Arg	Gly	Gly	Ala	Ala	Thr	Lys	Ala	Gly	
75																

cag	gag	gat	gtc	cca	cct	tct	acg	aaa	ggt	ctg	gaa	gca	gcc	tct	gcc	402
Gln	Glu	Asp	Ala	Pro	Pro	Ser	Thr	Lys	Gly	Leu	Glu	Ala	Ala	Ser	Ala	
90																

gcc	gag	gct	gac	agc	agc	cag	aaa	aat	ggc	tgt	cag	ctt	gga	gag	450
Ala	Glu	Ala	Ala	Asp	Ser	Ser	Gln	Lys	Asn	Gly	Cys	Gln	Leu	Gly	Glu
110															

ccc	cgt	ggc	cct	gct	ggg	cag	aag	gct	cta	gaa	gcc	tgt	ggc	gca	ggg	498
Pro	Arg	Gly	Pro	Ala	Gly	Gln	Lys	Ala	Leu	Glu	Ala	Cys	Gly	Ala	Gly	
125																

ggc	ttg	ggg	tct	cag	atg	ata	ccg	ggg	aag	ggc	aag	gaa	gtg	acg	546
Gly	Leu	Gly	Ser	Gln	Met	Ile	Pro	Gly	Lys	Lys	Gly	Ala	Lys	Glu	Val
140															

act	aaa	aaa	cgc	gcc	atc	tcg	gca	gca	gtg	gaa	aag	gag	gga	gaa	gca	594
Thr	Lys	Arg	Ala	Ile	Ser	Ala	Ala	Val	Glu	Lys	Glu	Gly	Glu	Ala	Ala	
155																

ggg	gct	gct	gtc	atg	gag	gaa	aag	aag	gtt	cag	aag	gaa	aaa	aag	gtg	642
Gly	Ala	Ala	Met	Glu	Glu	Lys	Lys	Val	Val	Gln	Lys	Glu	Lys	Lys	Val	

D00260 = 95/22960

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aat gcc cag gct gac agg gcc ttc ctt cag ctt gag cgc aag ttt ggc				786
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cgc atg cga agg ctc cac atg cag cgc aga agt ttc att atc cag aat				834
Arg Met Arg Arg Leu His Met Gln Arg Arg Ser Phe Ile Ile Gln Asn				
235	240	245		
atc cca ggt ttc tgg gtt act gcc ttt cga aac cac ccc cag ctg tca				882
Ile Pro Gly Phe Trp Val Thr Ala Phe Arg Asn His Pro Gln Leu Ser				
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cct atg atc agt ggc caa gat gaa gac atg ctg agg tac atg atc aat				930
Pro Met Ile Ser Gly Gln Asp Glu Asp Met Leu Arg Tyr Met Ile Asn				
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Leu Glu Val Glu Leu Lys His Pro Arg Ala Gly Cys Lys Phe Lys				
285	290	295		
ttc atc ttt cag ggc aac ccc tac ttc cga aat gag ggg ctt gtc aag				1026
Phe Ile Phe Gln Gly Asn Pro Tyr Phe Arg Asn Glu Gly Leu Val Lys				
300	305	310		
gaa tat gaa cgc aga tcc tct ggc cgg gtg gtg tct ctt tcc act cca				1074
Glw Tyr Glu Arg Arg Ser Ser Gly Arg Val Val Ser Leu Ser Thr Pro				
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Ile Arg Trp His Arg Gly Gln Asp Pro Gln Ala His Ile His Arg Asn				
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agc ctt cta gaa ttc gac aga att gca gag att atc aaa gga gaa ctg				1218
Ser Leu Leu Glu Phe Asp Arg Ile Ala Glu Ile Ile Lys Gly Glu Leu				
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Trp Pro Asn Pro Leu Gln Tyr Tyr Leu Met Gly Glu Gly Pro Arg Arg				
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Gly Ile Arg Gly Pro Pro Arg Gln Pro Val Glu Ser Ala Arg Ser Phe				
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Arg Phe Gln Ser Gly				
410				

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Thr Gly Gly Ser Leu Glu Thr Val Ala Glu Gly Gly Ala Ser Gln
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Asp Pro Val Asp Cys Gly Pro Ala Leu Arg Val Pro Val Ala Gly Ser
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Arg Gly Gly Ala Ala Thr Lys Ala Gly Gln Glu Asp Ala Pro Pro Ser
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Thr Lys Gly Leu Glu Ala Ala Ser Ala Ala Glu Ala Ala Asp Ser Ser
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Gln Lys Asn Gly Cys Gln Leu Gly Glu Pro Arg Gly Pro Ala Gly Gln
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Lys Ala Leu Glu Ala Cys Gly Ala Gly Leu Gly Ser Gln Met Ile
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Pro Gly Lys Lys Ala Lys Glu Val Thr Thr Lys Lys Arg Ala Ile Ser
145 150 155 160

Ala Ala Val Glu Lys Glu Gly Glu Ala Gly Ala Ala Met Glu Glu Lys
165 170 175

Lys Val Val Gln Lys Glu Lys Lys Val Ala Gly Gly Val Lys Glu Glu
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Thr Arg Pro Arg Ala Pro Lys Ile Asn Asn Cys Met Asp Ser Leu Glu
195 200 205

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225 230 235 240

Gln Arg Arg Ser Phe Ile Ile Gln Asn Ile Pro Gly Phe Trp Val Thr
245 250 255

Ala Phe Arg Asn His Pro Gln Leu Ser Pro Met Ile Ser Gly Gln Asp
260 265 270

Glu Asp Met Leu Arg Tyr Met Ile Asn Leu Glu Val Glu Glu Leu Lys
275 280 285

His Pro Arg Ala Gly Cys Lys Phe Lys Phe Ile Phe Gln Gly Asn Pro
290 295 300

Tyr Phe Arg Asn Glu Gly Leu Val Lys Glu Tyr Glu Arg Arg Ser Ser
305 310 315 320

Gly Arg Val Val Ser Leu Ser Thr Pro Ile Arg Trp His Arg Gly Gln
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Asp Pro Gln Ala His Ile His Arg Asn Arg Glu Gly Asn Thr Ile Pro
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355 360 365

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gcc gcc aaa tgt tta ctg gag cat ggt gcc aac cca gcg ctg agg aat 144
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cga aaa gga cag gta cca gcg gaa gtg gtc cca gac ccc atg gac atg 192
Arg Lys Gly Gln Val Pro Ala Glu Val Val Pro Asp Pro Met Asp Met
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tcc ctt gac aag gca gag gca gcc ctg gtg gcc aag gaa ttg cgg acg 240
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Leu Leu Glu Glu Ala Val Pro Leu Ser Cys Thr Leu Pro Lys Val Thr
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Ser Thr Pro Arg Thr Pro Arg Met Asp Phe Ser Arg Val Thr Gly Lys	
195 200 205	

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Leu	Gly	Ser	Leu	Gln	Gln	Arg	Glu	Gly	Ala	Lys	Ala	Glu	Val	Gly	Asp	
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 Arg Lys Gly Gln Val Pro Ala Glu Val Val Pro Asp Pro Met Asp Met
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 Ser Leu Asp Lys Ala Glu Ala Ala Leu Val Ala Lys Glu Leu Arg Thr
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 Leu Leu Glu Glu Ala Val Pro Leu Ser Cys Thr Leu Pro Lys Val Thr
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 Leu Pro Asn Tyr Asp Asn Val Pro Gly Asn Leu Met Leu Ser Ala Leu
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 Gly Leu Arg Leu Gly Asp Arg Val Leu Leu Asp Gly Gln Lys Thr Gly
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 Thr Leu Arg Phe Cys Gly Thr Thr Glu Phe Ala Ser Gly Gln Trp Val
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 Gly Val Glu Leu Asp Glu Pro Glu Gly Lys Asn Asp Gly Ser Val Gly
 145 150 155 160
 Gly Val Arg Tyr Phe Ile Cys Pro Pro Lys Gln Gly Leu Phe Ala Ser
 165 170 175
 Val Ser Lys Val Ser Lys Ala Val Asp Ala Pro Pro Ser Ser Val Thr
 180 185 190

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Ser Thr Pro Arg Thr Pro Arg Met Asp Phe Ser Arg Val Thr Gly Lys
 195 200 205

Gly Arg Arg Glu His Lys Gly Lys Lys Lys Ser Pro Ser Ser Pro Ser
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Leu Gly Ser Leu Gln Gln Arg Glu Gly Ala Lys Ala Glu Val Gly Asp
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Pro Pro Gly Gly Asp Phe Ser Asp Pro Val Thr Ser Ala Thr Leu Gly
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Ile Val Gln Val Phe Trp Gly Leu Asp Lys Lys Leu Ala Gln Arg Lys
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cac ttc ccg tcc gtc aac tgg ctc att agc tac agc aag tac atg cgc 336
His Phe Pro Ser Val Asn Trp Leu Ile Ser Tyr Ser Lys Tyr Met Arg
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 210 215 220

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<213> *Rattus* sp.

<400> 59
Ala Asp Ser Thr Ser Arg Trp Ala Glu Ala Leu Arg Glu Ile Ser Gly
1 5 10 15

Arg Leu Ala Glu Met Pro Ala Asp Ser Gly Tyr Pro Ala Tyr Leu Gly
20 25 30

Ala Arg Leu Ala Ser Phe Tyr Glu Arg Ala Gly Arg Val Lys Cys Leu
35 40 45

Gly Asn Pro Glu Arg Glu Gly Ser Val Ser Ile Val Gly Ala Val Ser

50	55	60
Pro Pro Gly Gly Asp Phe Ser Asp Pro Val Thr Ser Ala Thr Leu Gly		
65 65 70 75 80		
Ile Val Gln Val Phe Trp Gly Leu Asp Lys Lys Leu Ala Gln Arg Lys		
85 90 95		
His Phe Pro Ser Val Asn Trp Leu Ile Ser Tyr Ser Lys Tyr Met Arg		
100 105 110		
Ala Leu Asp Glu Tyr Tyr Asp Lys His Phe Thr Glu Phe Val Pro Leu		
115 120 125		
Arg Thr Lys Ala Lys Glu Ile Leu Gln Glu Glu Asp Leu Ala Glu		
130 135 140		
Ile Val Gln Leu Val Gly Lys Ala Ser Leu Ala Glu Thr Asp Lys Ile		
145 150 155 160		
Thr Leu Glu Val Ala Lys Leu Ile Lys Asp Asp Phe Leu Gln Gln Asn		
165 170 175		
Gly Tyr Thr Pro Tyr Asp Arg Phe Cys Pro Phe Tyr Lys Thr Val Gly		
180 185 190		
Met Leu Ser Asn Met Ile Ser Phe Tyr Asp Met Ala Arg Arg Ala Val		
195 200 205		
Glu Thr Thr Ala Gln Ser Asp Asn Lys Ile Thr Trp Ser Ile Ile Arg		
210 215 220		
Glu His Met Gly Glu Ile Leu Tyr Lys Leu Ser Ser Met Lys Phe Lys		
225 230 235 240		
Asp Pro Val Lys Asp Gly Glu Ala Lys Ile Lys Ala Asp Tyr Ala Gln		
245 250 255		
Leu Leu Glu Asp Met Gln Asn Ala Phe Arg Ser Leu Glu Asp		
260 265 270		

<210> 60
<211> 1489
<212> DNA
<213> Rattus sp.

<220>
<221> CDS
<222> (1)..(1053)

<400> 60
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Ala Arg Leu Pro Ala Pro Glu His Ala Arg Gln Gln Pro Leu Leu Ser
1 5 10 15

ggc cct gag ccc gga tcg tcc gcc ccg gtt cca gtc ggc gtg gcc 96
Gly Pro Glu Pro Gly Ser Ser Ala Arg Val Pro Val Pro Gly Val Ala
20 25 30

agt agg cgg cag ccg cga ggc aag cca ccc agc ggg gac ggc ctg 144

09570756 • 022200

Ser Arg Arg Gln Pro Arg Gly Gly Lys Pro Pro Ser Gly Asp Gly Leu
 35 40 45

gag tcg ggc ccc tct cca cgc ccc ctt ctc cac gcg cgc ggg gag gca 192
 Glu Ser Gly Pro Ser Pro Arg Pro Leu Leu His Ala Arg Gly Glu Ala
 50 55 60

ggg ctc cac cgc cag tct gga agg gtt cca cat aca gga acg gcc tac 240
 Gly Leu His Arg Gln Ser Gly Arg Val Pro His Thr Gly Thr Ala Tyr
 65 70 75 80

ttc gca gat gag ccc acc gag gct cag gct ccg ggc gga ttc tgc gtg 288
 Phe Ala Asp Glu Pro Thr Glu Ala Gln Ala Pro Gly Gly Phe Cys Val
 85 90 95

tca ccc tcg ctc ctt ggg gtc cgc tgg ccg gcc tgt gcc acc cgg acg 336
 Ser Pro Ser Leu Leu Gly Val Arg Trp Pro Ala Cys Ala Thr Arg Thr
 100 105 110

ccc ggc tca ctg cct ctg tct ccc cca tca gcg cag ccc cgg acg cta 384
 Pro Gly Ser Leu Pro Leu Ser Pro Pro Ser Ala Gln Pro Arg Thr Leu
 115 120 125

tgg ccc acc cct cca gct ggc ccc tcg agt agg atq gta gca cgt aac 432
 Trp Pro Thr Pro Pro Ala Gly Pro Ser Ser Arg Met Val Ala Arg Asn
 130 135 140

cag gtg gca gcc gac aat gcg atc tcc ccg gca tca gag ccc cga cgg 480
 Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala Ser Glu Pro Arg Arg
 145 150 155 160

cgg cca gag cca tcc tcg tcc tcg tct tcg tcc tcg ccg ggc gcc ccc 528
 Arg Pro Glu Pro Ser Ser Ser Ser Ser Pro Ala Ala Pro
 165 170 175

gcg cgt ccc cgg ccc tgc ccg gtg gtc gcc ccg gct ccg ggc gac 576
 Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala Pro Ala Pro Gly Asp
 180 185 190

act cac ttc cgc acc ttc cgc tcc cac tct gat tac ccg cgc atc acg 624
 Thr His Phe Arg Thr Phe Arg Ser His Ser Asp Tyr Arg Arg Ile Thr
 195 200 205

ccg acc agc gct ctc ctg gac gcc tgc ggc ttc tac tgg gga ccc ctg 672
 Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr Trp Gly Pro Leu
 210 215 220

agc gtg cat ggg ggc cac gaa ccg ctg cgt gcc gag ccc gtg ggc acc 720
 Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu Pro Val Gly Thr
 225 230 235 240

ttc ttg gtg cgc gac agt cgc cag ccg aac tgc ttc ttc gcg ctc acg 768
 Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe Phe Ala Leu Ser
 245 250 255

gtg aag atg gct tcg ggc ccc acg acg att cgt gtg cac ttc cag gcc 816
 Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val His Phe Gln Ala
 260 265 270

DRAFT - 95% IDENTICAL

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ggc cgc ttc cac ctg gac ggc agc cgc gag acc ttc gac tgc ctc ttc 864
Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr Phe Asp Cys Leu Phe
     275           280           285

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gag ctg ctg gag cac tac gtg gcg gcg ccg cgc cgc atg ttg ggg gcc 912
Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg Met Leu Gly Ala
   290      295      300

```

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cca ctg cgc cag cgc cgc gtg cgg ccg ctg cag gag ctg tgt cgc cag  960
Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu Leu Cys Arg Gln
305          310          315          320

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cgc atc gtg gcc gtg ggt cgcc gag aac ctg gca cgcc atcc cct ctt    1008
Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu Ala Arg Ile Pro Leu
          325           330           335

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aac ccg gta ctc cgt gac tac ctg agt tcc ttc ccc ttc cag atc      1053
Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro Phe Gln Ile
          340        345        350

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tgaccggctg ccggcgtgcc cgccgcattt agtggggagcg ctttattttt tttttttttt 1113
aattttttt atttttctgg aaccacgtgg gagccccccc cgccttagtc ggaggggagt 1173
ggtgtggagg gtgagatgcc tccccacttct ggctggagac cttatccgc ctctcgaaaa 1233
gcctcccttc ctgggtctcc ctccgggtcc ccctgggtgt agcagcttgt gtctggggcc 1293
aggacctgaa ctccacgcct acctctccat gtttacatgt tcccaatgtt ttgcacaaaa 1353
ccaggggtgg ggggggggtct ctgggttcat ttttctgttgcagaatat tctatTTTtat 1413
atTTTttatccat ccagtttaga taataaaactt tattatgaaa gttttttttttaaagaaaaaa 1473
aaaaaaaaaaaaaaa 1489

<210> 61
<211> 351
<212> PRT
<213> *Battus* sp.

<400> 61
Ala Arg Leu Pro Ala Pro Glu His Ala Arg Gln Gln Pro Leu Leu Ser
1 5 10 15

Gly Pro Glu Pro Gly Ser Ser Ala Arg Val Pro Val Pro Gly Val Ala
20 25 30

Ser Arg Arg Gln Pro Arg Gly Gly Lys Pro Pro Ser Gly Asp Gly Leu
35 40 45

Glu Ser Gly Pro Ser Pro Arg Pro Leu Leu His Ala Arg Gly Glu Ala
50 55 60

Gly Leu His Arg Gln Ser Gly Arg Val Pro His Thr Gly Thr Ala Tyr
 65 70 75 80

Phe Ala Asp Glu Pro Thr Glu Ala Gln Ala Pro Gly Gly Phe Cys Val
85 90 95

Ser Pro Ser Leu Leu Gly Val Arg Trp Pro Ala Cys Ala Thr Arg Thr
100 105 110

Pro Gly Ser Leu Pro Leu Ser Pro Pro Ser Ala Gln Pro Arg Thr Leu
115 120 125

Trp Pro Thr Pro Pro Ala Gly Pro Ser Ser Arg Met Val Ala Arg Asn
130 135 140

Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala Ser Glu Pro Arg Arg
145 150 155 160

Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser Pro Ala Ala Pro
165 170 175

Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala Pro Ala Pro Gly Asp
180 185 190

Thr His Phe Arg Thr Phe Arg Ser His Ser Asp Tyr Arg Arg Ile Thr
195 200 205

Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe Tyr Trp Gly Pro Leu
210 215 220

Ser Val His Gly Ala His Glu Arg Leu Arg Ala Glu Pro Val Gly Thr
225 230 235 240

Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys Phe Phe Ala Leu Ser
245 250 255

Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg Val His Phe Gln Ala
260 265 270

Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr Phe Asp Cys Leu Phe
275 280 285

Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg Arg Met Leu Gly Ala
290 295 300

Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln Glu Leu Cys Arg Gln
305 310 315 320

Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu Ala Arg Ile Pro Leu
325 330 335

Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe Pro Phe Gln Ile
340 345 350

<210> 62

<211> 1194

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (130)..(765)

<400> 62

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 cccccgggtcc cccggccggcgc gcagccccgg acgctatggc ccacccctcc agctggcccc 120
 tcgtaggg atg gta gca cgt aac cag gtg gca gcc gac aat gcg atc tcc 171
 Met Val Ala Arg Asn Gln Val Ala Ala Asp Asn Ala Ile Ser
 1 5 10
 ccg gca tca gag ccc cga cgg cgg cca gag cca tcc tcc tcc tcc tct 219
 Pro Ala Ser Glu Pro Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser
 15 20 25 30
 tcg tcc tcc ccc ccc ccc ccc ccc ccc ccc ccc tcc tcc tcc tcc tcc tcc 267
 Ser Ser Ser Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Val Val
 35 40 45
 ccg gcc ccc gct ccc ggc gac act cac ttc ccc acc tcc ccc tcc tcc cac 315
 Pro Ala Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His
 50 55 60
 tct gat tac ccc ccc atc acg ccc acc agc gct ccc ccc gac gcc gcc tcc 363
 Ser Asp Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys
 65 70 75
 ggc ttc tac tgg gga ccc ctg agc gtg cat ggg ggc cac gaa cgg cgg 411
 Gly Phe Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu
 80 85 90
 cgt gcc gag ccc gtg ggc acc ttc ttg gtg ccc gac agt ccc ccc ccc ccc 459
 Arg Ala Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg
 95 100 105 110
 aac tgc ttc ttc ggc ctc agc gtg aag atg gct tcc ggc ccc acc acc 507
 Asn Cys Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser
 115 120 125
 att cgt gtg cac ttc cag gcc ggc ccc ttc cac ctg gac ggc agc ccc 555
 Ile Arg Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg
 130 135 140
 gag acc ttc gac tgc ctc ttc gag ctg ctg gag cac tac gtg ggc ggc 603
 Glu Thr Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala
 145 150 155
 ccg ccc ccc atg ttg ggg gcc cca ctg ccc ccc ccc ccc ccc ccc ccc 651
 Pro Arg Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro
 160 165 170
 ctg cag gag ctg tgt ccc ccc atc gtg gcc gcc gtg ggt ccc ccc 699
 Leu Gln Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu
 175 180 185 190
 aac ctg gca ccc atc ccc aac ccc gta ccc ccc gac tac ctg agt 747
 Asn Leu Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser
 195 200 205
 tcc ttc ccc ttc cag atc tgaccggctc cccggctgc cccggattaa 795
 Ser Phe Pro Phe Gln Ile
 210

agtgggagcg ctttattttt aattttttt atttttctgg aaccacgtgg 855
 gagccctccc cgcttaggtc ggagggagtg ggtgtggagg gtgagatgcc tccccacttc 915
 ggctggagac ctatccccgc ctctcgaaaa gcctccctc ctgggtgtcc ctcccggtcc 975
 ccctgggttg agcagcttgt gtctggggcc aggacctgaa ctccacgcct acctctccat 1035
 gtttacatgt tcccagatata tttgcacaaa ccaggggtgg gggagggtct ctgggttcat 1095
 ttttctgtgt tgcaaatat tctattttat atttttacat ccagtttaga taataaactt 1155
 tattatgaaa gttttttttt taaaaaaaaaaaaaaa 1194

<210> 63
<211> 212
<212> PRT
<213> Rattus sp.

<400> 63
 Met Val Ala Arg Asn Gln Val Ala Ala Asp Asn Ala Ile Ser Pro Ala
 1 5 10 15
 Ser Glu Pro Arg Arg Arg Pro Glu Pro Ser Ser Ser Ser Ser Ser
 20 25 30
 Ser Pro Ala Ala Pro Ala Arg Pro Arg Pro Cys Pro Val Val Pro Ala
 35 40 45
 Pro Ala Pro Gly Asp Thr His Phe Arg Thr Phe Arg Ser His Ser Asp
 50 55 60
 Tyr Arg Arg Ile Thr Arg Thr Ser Ala Leu Leu Asp Ala Cys Gly Phe
 65 70 75 80
 Tyr Trp Gly Pro Leu Ser Val His Gly Ala His Glu Arg Leu Arg Ala
 85 90 95
 Glu Pro Val Gly Thr Phe Leu Val Arg Asp Ser Arg Gln Arg Asn Cys
 100 105 110
 Phe Phe Ala Leu Ser Val Lys Met Ala Ser Gly Pro Thr Ser Ile Arg
 115 120 125
 Val His Phe Gln Ala Gly Arg Phe His Leu Asp Gly Ser Arg Glu Thr
 130 135 140
 Phe Asp Cys Leu Phe Glu Leu Leu Glu His Tyr Val Ala Ala Pro Arg
 145 150 155 160
 Arg Met Leu Gly Ala Pro Leu Arg Gln Arg Arg Val Arg Pro Leu Gln
 165 170 175
 Glu Leu Cys Arg Gln Arg Ile Val Ala Ala Val Gly Arg Glu Asn Leu
 180 185 190
 Ala Arg Ile Pro Leu Asn Pro Val Leu Arg Asp Tyr Leu Ser Ser Phe
 195 200 205
 Pro Phe Gln Ile

D0476759 + 0922700

210

<210> 64
 <211> 600
 <212> DNA
 <213> Rattus sp.

<220>
 <221> CDS
 <222> (52)..(336)

<400> 64
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 Met Pro
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tcc caa atg gag cat gcc atg gaa acc atg atg ctt aca ttt cac agg 105
 Ser Gln Met Glu His Ala Met Glu Thr Met Met Leu Thr Phe His Arg
 5 10 15

ttt gca ggg gaa aaa aac tac ttg aca aag gag gac ctg aga gtg ctc 153
 Phe Ala Gly Glu Lys Asn Tyr Leu Thr Lys Glu Asp Leu Arg Val Leu
 20 25 30

atg gaa agg gag ttc cct ggg ttt ttg gaa aat caa aag gac cct ctg 201
 Met Glu Arg Glu Phe Pro Gly Phe Leu Glu Asn Gln Lys Asp Pro Leu
 35 40 45 50

gct gtg gac aaa ata atg aaa gac ctg gac cag tgc gta gat gga aaa 249
 Ala Val Asp Lys Ile Met Lys Asp Leu Asp Gln Cys Arg Asp Gly Lys
 55 60 65

gtg ggc ttc cag agc ttt cta tca cta gtg gcg ggg ctc atc att gca 297
 Val Gly Phe Gln Ser Phe Leu Ser Leu Val Ala Gly Leu Ile Ile Ala
 70 75 80

tgc aat gac tat ttt gta gta cac atg aag cag aag taggccaact 346
 Cys Asn Asp Tyr Phe Val Val His Met Lys Gln Lys Lys
 85 90 95

ggggcccttg taccacacc ttgtatgcgtc ctctccatg gggtaactg aggaatctgc 406

cccaactgttt cctgtgagca gatcaggacc cttaggaat gtgcaaataa catccaactc 466

caattcgcaca agcagagaaaa gaaaagttaa tccaatgaca gaggagctt cgagtttat 526

atgtttgcata tccgggttgcc ctcaataaaag aaagtctttt ttttaagtt ccgaaaaaaaa 586

aaaaaaaaaaaa aaaa 600

<210> 65
 <211> 95
 <212> PRT
 <213> Rattus sp.

<400> 65
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 1 5 10 15

D002365-95/02950

His	Arg	Phe	Ala	Gly	Glu	Lys	Asn	Tyr	Leu	Thr	Lys	Glu	Asp	Leu	Arg
20									25					30	

Val	Leu	Met	Glu	Arg	Glu	Phe	Pro	Gly	Phe	Leu	Glu	Asn	Gln	Lys	Asp
35									40					45	

Pro	Leu	Ala	Val	Asp	Lys	Ile	Met	Lys	Asp	Leu	Asp	Gln	Cys	Arg	Asp
50									55					60	

Gly	Lys	Val	Gly	Phe	Gln	Ser	Phe	Leu	Ser	Leu	Val	Ala	Gly	Leu	Ile
65									75					80	

Ile	Ala	Cys	Asn	Asp	Tyr	Phe	Val	Val	His	Met	Lys	Gln	Lys	Lys	
85									90					95	

<210> 66

<211> 639

<212> DNA

<213> Rattus sp.

<220>

<221> CDS

<222> (1)...(636)

<400> 66

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Met	Ala	Tyr	Ala	Tyr	Leu	Phe	Lys	Tyr	Ile	Ile	Ile	Gly	Asp	Thr	Gly
1					5				10					15	

gtt	ggg	aaa	tcg	tgc	tta	ttg	cta	cag	ttt	aca	gac	aag	agg	ttt	cag
Val	Gly	Lys	Ser	Cys	Leu	Leu	Leu	Gln	Phe	Thr	Asp	Lys	Arg	Phe	Gln
					20				25					30	

ccg	gtg	cat	gac	ctc	aca	att	ggt	gta	gag	ttt	ggt	gct	cga	atg	ata
Pro	Val	His	Asp	Leu	Thr	Ile	Gly	Val	Glu	Phe	Gly	Ala	Arg	Met	Ile
					35				40					45	

acc	att	gat	ggg	aaa	cag	ata	aaa	ctc	cag	atc	tgg	gat	aaa	gca	ggg
Thr	Ile	Asp	Gly	Lys	Gln	Ile	Lys	Leu	Gln	Ile	Trp	Asp	Thr	Ala	Gly
					50				55					60	

cag	gag	tcc	ttt	cgt	tct	atc	aca	agg	tca	tat	tac	aga	ggt	gca	gog
Gln	Glu	Ser	Phe	Arg	Ser	Ile	Thr	Arg	Ser	Tyr	Tyr	Arg	Gly	Ala	Ala
					65				70					80	

ggg	gct	tta	cta	gtg	tat	gat	att	aca	agg	aga	gac	acg	ttc	aac	cac
Gly	Ala	Leu	Leu	Val	Tyr	Asp	Ile	Thr	Arg	Arg	Asp	Thr	Phe	Asn	His
					85				90					95	

ttg	aca	acc	tgg	tta	gaa	gac	gcc	cgt	cag	cat	tcc	aat	tcc	aac	atg
Leu	Thr	Thr	Trp	Leu	Glu	Asp	Ala	Arg	Gln	His	Ser	Asn	Ser	Asn	Met
					100				105					110	

gtc	atc	atg	ctt	att	gga	aat	aaa	agt	gac	tta	gaa	tct	agg	aga	gaa
Val	Ile	Met	Leu	Ile	Gly	Asn	Lys	Ser	Asp	Leu	Glu	Ser	Arg	Arg	Glu
					115				120					125	

gtg	aaa	aag	gaa	gaa	ggt	gaa	gct	ttt	gca	cga	gag	cat	gga	ctt	atc
Val	Lys	Lys	Glu	Glu	Gly	Glu	Ala	Phe	Ala	Arg	Glu	His	Gly	Leu	Ile
					130				135					140	

00670756 - 0527080

ttc atg gaa act tot gcc aag act gct tct aat gta gag gag gca ttt
 Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
 145 150 155 160
 att aac aca gca aaa gaa att tat gaa aaa atc caa gaa ggg gtc ttt
 Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
 165 170 175
 gac att aat aat gag gca aac ggc atc aaa att ggc cct cag cat gct
 Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
 180 185 190
 gct acc aat gca tct cac gga ggc aac caa gga ggg cag cag gca ggg
 Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
 195 200 205
 gga ggc tgc tgc tga
 Gly Gly Cys Cys
 210
 <210> 67
 <211> 212
 <212> PRT
 <213> Rattus sp.
 <400> 67
 Met Ala Tyr Ala Tyr Leu Phe Lys Tyr Ile Ile Ile Gly Asp Thr Gly
 1 5 10 15
 Val Gly Lys Ser Cys Leu Leu Leu Gln Phe Thr Asp Lys Arg Phe Gln
 20 25 30
 Pro Val His Asp Leu Thr Ile Gly Val Glu Phe Gly Ala Arg Met Ile
 35 40 45
 Thr Ile Asp Gly Lys Gln Ile Lys Leu Gln Ile Trp Asp Thr Ala Gly
 50 55 60
 Gln Glu Ser Phe Arg Ser Ile Thr Arg Ser Tyr Tyr Arg Gly Ala Ala
 65 70 75 80
 Gly Ala Leu Leu Val Tyr Asp Ile Thr Arg Arg Asp Thr Phe Asn His
 85 90 95
 Leu Thr Thr Trp Leu Glu Asp Ala Arg Gln His Ser Asn Ser Asn Met
 100 105 110
 Val Ile Met Leu Ile Gly Asn Lys Ser Asp Leu Glu Ser Arg Arg Glu
 115 120 125
 Val Lys Lys Glu Glu Gly Glu Ala Phe Ala Arg Glu His Gly Leu Ile
 130 135 140
 Phe Met Glu Thr Ser Ala Lys Thr Ala Ser Asn Val Glu Glu Ala Phe
 145 150 155 160
 Ile Asn Thr Ala Lys Glu Ile Tyr Glu Lys Ile Gln Glu Gly Val Phe
 165 170 175

Asp Ile Asn Asn Glu Ala Asn Gly Ile Lys Ile Gly Pro Gln His Ala
 180 185 190

Ala Thr Asn Ala Ser His Gly Gly Asn Gln Gly Gly Gln Gln Ala Gly
 195 200 205

Gly Gly Cys Cys
 210

<210> 68
 <211> 816
 <212> DNA
 <213> Rattus sp.

<220>
 <221> CDS
 <222> (1)..(813)

<400> 68

atg	gtc	ctg	ctc	aag	gaa	tat	cgg	gtc	atc	ctg	cct	gtg	tct	gta	gat	48
Met	Val	Leu	Leu	Lys	Glu	Tyr	Arg	Val	Ile	Leu	Pro	Val	Ser	Val	Asp	
1				5					10				15			

gag	tat	caa	gtg	ggg	cag	ctg	tac	tct	gtg	gct	gaa	gcc	agt	aaa	aat	96
Glu	Tyr	Gln	Val	Gly	Gln	Leu	Tyr	Ser	Val	Ala	Glu	Ala	Ser	Lys	Asn	
20				25									30			

gaa	act	ggt	ggg	gaa	ggt	gtg	gag	gtc	ctg	gtg	aac	gag	ccc	tac	144
Glu	Thr	Gly	Gly	Glu	Gly	Val	Glu	Val	Leu	Val	Asn	Glu	Pro	Tyr	
35				40							45				

gag	aag	gat	gat	ggc	gag	aaa	ggc	cag	tac	aca	cac	aag	atc	tac	cac	192
Glu	Lys	Asp	Asp	Gly	Glu	Lys	Gly	Gln	Tyr	Thr	His	Lys	Ile	Tyr	His	
50				55						60						

tta	cag	agc	aaa	gtt	ccc	acg	ttt	gtt	cga	atg	ctg	gcc	cca	gaa	ggc	240
Leu	Gln	Ser	Lys	Val	Pro	Thr	Phe	Val	Arg	Met	Leu	Ala	Pro	Glu	Gly	
65				70						75			80			

gcc	ctg	aat	ata	cat	gag	aaa	gcc	tgg	aat	gcc	tac	cct	tac	tgc	aga	288
Ala	Leu	Asn	Ile	His	Glu	Lys	Ala	Trp	Asn	Ala	Tyr	Pro	Tyr	Cys	Arg	
85				90						95						

acc	gtt	att	aca	aat	gag	tac	atg	aag	gaa	gac	ttt	ctc	att	aaa	att	336	
Thr	Val	Ile	Thr	Asn	Ile	His	Glu	Tyr	Met	Lys	Glu	Asp	Phe	Leu	Ile	Lys	Ile
100				105						110							

gaa	acc	tgg	cac	aag	cca	gac	ctt	ggc	acc	cag	gag	aat	gtg	cat	aaa	384
Glu	Thr	Trp	His	Lys	Pro	Asp	Leu	Gly	Thr	Gln	Glu	Asn	Val	His	Lys	
115				120						125						

ctg	gag	cct	gag	gca	tgg	aaa	cat	gtg	gaa	gct	ata	tat	ata	gac	atc	432
Leu	Glu	Pro	Glu	Ala	Trp	Lys	His	Val	Glu	Ala	Ile	Tyr	Ile	Asp	Ile	
130				135						140						

gct	gat	cga	agg	caa	gtt	acc	tgg	aag	gat	tac	aag	gca	gag	aaa	480
Ala	Asp	Arg	Ser	Gln	Val	Leu	Ser	Lys	Asp	Tyr	Lys	Ala	Glu	Asp	
145				150						155		160			

cca	gca	aaa	ttt	aaa	tct	atc	aaa	aca	gga	cga	gga	cca	ttg	ggc	ccg	528
-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

DRAFT/2005-052700

Pro Ala Lys Phe Lys Ser Ile Lys Thr Gly Arg Gly Pro Leu Gly Pro	165	170	175
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aat tgg aag caa gaa ctt gtc aat cag aag gac tgc cca tat atg tgt			576
Asn Trp Lys Gln Glu Leu Val Asn Gln Lys Asp Cys Pro Tyr Met Cys			
180	185	190	

gca tac aaa ctg gtt act gtc aag ttc aag tgg tgg ggc ttg cag aac			624
Ala Tyr Lys Leu Val Thr Val Lys Phe Lys Trp Trp Gly Leu Gln Asn			
195	200	205	

aaa gtg gaa aac ttt ata cat aag caa gag aag cgt ctg ttt aca aac			672
Lys Val Glu Asn Phe Ile His Lys Gln Glu Lys Arg Leu Phe Thr Asn			
210	215	220	

ttt cac agg cag ctg ttc tgt tgg ctt gat aaa tgg gtt gat ctg act			720
Phe His Arg Gln Leu Phe Cys Trp Leu Asp Lys Trp Val Asp Leu Thr			
225	230	235	240

atg gat gac att cgg agg atg gaa gaa gag acg aag aca cag ctg gat			768
Met Asp Asp Ile Arg Arg Met Glu Glu Thr Lys Arg Gln Leu Asp			
245	250	255	

gag atg aga caa aag gac ccc gtg aaa gga atg aca gca gat gac tag			816
Glu Met Arg Gln Lys Asp Pro Val Lys Gly Met Thr Ala Asp Asp			
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<212> DNA
<213> Simian sp.

<400> 69
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catgacttgc gaagggttgc aaatgtatgc agttctgatc gtcattgtgc tttttgttaa 180
attattggaa cagttgggc tgattgaagc aggttttagaa gacagcgtgg aagatgaact 240
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tgttgttaat gaagaaacct tcaaagatc ttactcgac ttctttccac agggagactc 420
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gtttgtatata atgaaagcaa tatacgacat gatggtaaa tggatatac ctgtcctcaa 660
agaagatgca cccagacaac acgtcgaaac atttttcag aaaaatggaca aaaataaaga 720

DRAFT/05/2000

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<210> 70
 <211> 229
 <212> PRT
 <213> Simian sp.

<400> 70
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Leu Phe Val Lys Leu Leu Glu Gln Phe Gly Leu Ile Glu Ala Gly Leu
20 25 30

Glu Asp Ser Val Glu Asp Glu Leu Glu Met Ala Thr Val Arg His Arg
35 40 45

Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser Lys Phe Thr Lys Lys
50 55 60

Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn Glu Cys Pro Ser Gly
65 70 75 80

Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr Ser Gln Phe Phe Pro
85 90 95

Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu Phe Asn Ala Phe Asp
100 105 110

Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp Phe Ile Lys Gly Leu
115 120 125

Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys Leu Asn Trp Ala Phe
130 135 140

Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile Thr Lys Glu Glu Met
145 150 155 160

Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met Gly Lys Cys Thr Tyr
165 170 175

Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His Val Glu Thr Phe Phe
180 185 190

Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val Thr Ile Asp Glu Phe
195 200 205

Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met Arg Ser Met Gln Leu
210 215 220

Phe Glu Asn Val Ile
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<210> 71

<211> 2259

<212> DNA

<213> Simian sp.

<400> 71

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ggcggtttcc tgttatgctca gaacagcacc aagcgcagca ttaaagagcg gctcatgaag 180

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gaactggaga tggccactgt caggcatcgg cctgaggccc ttgagcttct ggaagccag 300

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<211> 250
<212> PRT
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Ile Lys Glu Arg Leu Met Lys Leu Leu Pro Cys Ser Ala Ala Lys Thr
35 40 45

Ser Ser Pro Ala Ile Gln Asn Ser Val Glu Asp Glu Leu Glu Met Ala
50 55 60

Thr Val Arg His Arg Pro Glu Ala Leu Glu Leu Leu Glu Ala Gln Ser
65 70 75 80

Lys Phe Thr Lys Lys Glu Leu Gln Ile Leu Tyr Arg Gly Phe Lys Asn
85 90 95

Glu Cys Pro Ser Gly Val Val Asn Glu Glu Thr Phe Lys Glu Ile Tyr
100 105 110

Ser Gln Phe Phe Pro Gln Gly Asp Ser Thr Thr Tyr Ala His Phe Leu
115 120 125

Phe Asn Ala Phe Asp Thr Asp His Asn Gly Ala Val Ser Phe Glu Asp
130 135 140

Phe Ile Lys Gly Leu Ser Ile Leu Leu Arg Gly Thr Val Gln Glu Lys
145 150 155 160

Leu Asn Trp Ala Phe Asn Leu Tyr Asp Ile Asn Lys Asp Gly Tyr Ile
165 170 175

Thr Lys Glu Glu Met Leu Asp Ile Met Lys Ala Ile Tyr Asp Met Met
180 185 190

Gly Lys Cys Thr Tyr Pro Val Leu Lys Glu Asp Ala Pro Arg Gln His
195 200 205

Val Glu Thr Phe Phe Gln Lys Met Asp Lys Asn Lys Asp Gly Val Val
210 215 220

Thr Ile Asp Glu Phe Ile Glu Ser Cys Gln Lys Asp Glu Asn Ile Met
225 230 235 240

Arg Ser Met Gln Leu Phe Glu Asn Val Ile
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<210> 73
<211> 10
<212> PRT
<213> Simian sp.

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Ser Asn Ala Lys Ala Val Glu Thr Asp Val
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